Health Evidence Review Commission's Value-based Benefits Subcommittee

June 12, 2014

8:30 AM

Meridian Park Hospital
Community Health Education Center, Room 117B & C
19300 SW 65th Avenue, Tualatin, OR 97062

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
June 12, 2014
8:30am - 1:00pm
Meridian Park Room 117B&C
Community Health Education Center
Tualatin, OR 97062
A working lunch will be served at approximately 12:00 PM
All times are approximate

I. Call to Order, Roll Call, Approval of Minutes – Lisa Dodson 8:30 AM

II. Staff report – Ariel Smits, Cat Livingston, Darren Coffman 8:35 AM

III. New discussion items – Ariel Smits 8:45 AM

A. Hearing loss issues
    A. Biennial review deletion of audiant bone conductor for conductive hearing loss line
    B. Unilateral hearing loss
    C. Bone anchored hearing aids
B. Physical therapy for urinary incontinence

IV. Previous Discussion Items – Ariel Smits, Cat Livingston 9:45 AM

A. Electroconvulsive therapy (ECT) guideline
B. Applied behavioral analysis for autism spectrum disorders
C. Gender dysphoria
    A. Cross sex hormone therapy
    B. Sex reassignment surgery

V. Guidelines – Ariel Smits, Cat Livingston 11:15 AM

A. Bariatric surgery guideline clarifications
B. Rehabilitation guideline clarifications
C. Lymphedema guideline
D. Treatment of hepatitis C

VI. Public comment 12:55 PM

VII. Adjournment – Lisa Dodson 1:00 PM

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission in June 2014

For specific coding recommendations and guideline wording, please see the text of the 05/08/14 VbBS minutes.

CODE MOVEMENT

- A surgical code was added to the colon cancer line
- A surgical code was added to the vascular insufficiency of intestines line
- Open and closed hip fracture diagnoses were combined on the hip fracture line
- Transurethral prostatic implants were added for treatment of benign prostatic hypertrophy
- Multiple surgical codes were removed from the covered sleep apnea line

ITEMS CONSIDERED BUT NO CHANGES MADE

- The addition of cross-sex hormone therapy and sex reassignment surgery as treatments for gender dysphoria were discussed, but no decisions were made. This topic will be readdressed at the June 2014 meeting.
- The fluoride varnish guideline was reviewed but no changes made
- Electronic tumor treatment fields were not added for treatment of recurrent glioblastoma
- A new guideline regarding electroconvulsive therapy (ECT) was discussed, and will be further discussed at an upcoming meeting
- The structure of the low back pain lines was discussed, and will be readdressed at a future meeting
- Changes to the fluoride varnish guideline were discussed but no changes made

GUIDELINE CHANGES

- The rehabilitation guideline was extensively revised to reflect criteria for rehabilitation services rather than limits on the number of visits.
- The sleep apnea guideline was revised to further define daytime sleepiness and to specify that tonsillectomy/adenoidectomy surgical codes on that line are for treatment of children only.
- A new diagnostic guideline was added specifying that computer aided mammography (screening and diagnostic) is not a covered service

BIENNIAL REVIEW

- The diagnosis codes for injuries to the major blood vessels of the neck were moved from one covered line to a more appropriate covered line
- A new lymphedema line was created and prioritized into the covered region of the Prioritized List
- A new line for miscellaneous conditions requiring no treatment was created and prioritized to the last line on the Prioritized List
- The somatization and factitious disorder lines were merged and prioritized into the non-covered region of the Prioritized List

MINUTES

VALUE-BASED BENEFITS SUBCOMMITTEE

Clackamas Community College, Room 111-112
Wilsonville Training Center
29353 SW Town Center Loop E
Wilsonville, Oregon 97070
May 8, 2014

Members Present: Lisa Dodson, MD, Chair; Kevin Olson, MD, Vice-chair (left 1 PM); James Tyack, DMD; David Pollack, MD; Susan Williams, MD (arrived 8:50 AM); Mark Gibson (left 1:15 PM); Irene Croswell, RPh; Laura Ocker, LAc.

Members Absent: None

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Jason Gingerich; Denise Taray.

Also Attending: Jesse Little, OHA Actuarial Services Unit; Brian Nieubuurt, OHA; Danielle Askini, Peter Molof, Aubrey Harrison and Maura Roche, Basic Rights Oregon; Megan Bird, MD, Legacy Health Systems; Kathleen Klemann, FamilyCare; Bruce Boston, MD, OHSU; Shane Jackson, OR ABA; Brenna Legaard; Tobi Rates, Autism Society of Oregon; Susan Bamberger, Oregon Physical Therapy Association; Bridget Kiene, American Cancer Society; John Beckwith, PT, Sacred Heart Medical Center; Tim Baxter, Lane County Legal Aid.

Roll Call/Minutes Approval/Staff Report

The meeting was called to order at 8:35 am and roll was called. Minutes from the March 2014 VbBS meeting were reviewed and approved without changes.

MOTION: To approve the March 2014 VbBS minutes as presented. CARRIES 7-0 (Williams absent).

> **Action:** HERC staff will post the approved minutes on the website as soon as possible.

Smits reported that ICD-10 implementation has been delayed until at least October 1, 2015 by CMS. The October 1, 2014 Prioritized List is in ICD-10 format. Staff has met with HERC leadership and decided to keep the previously adopted October 1, 2014 List and add the ICD-9 codes back to the lines, making the List "bilingual" with both ICD-9 and ICD-10 codes on each line. There was no objection or discussion about this plan.

Smits announced that Dr. Holly Jo Hodges from Trillium Healthcare will be joining the VbBS as the medical director/CCO representative beginning with the June, 2014 VbBS meeting. Dr. Lisa Dodson will be stepping down as Chair and resigning after the June,

2014 VbBS meeting due to a move to Wisconsin. Her service has been exemplary and her leadership will be sorely missed.

Note: All line numbers in these minutes reflect the understanding at the time of this meeting that they would go into effect on October 1, 2014 with the implementation of the new biennial list. At the June 12, 2014 meeting the subcommittee will discuss implementing the biennial list on January 1, 2015 instead, as there is no longer an need to tie it to implementation of the ICD-10-CM codeset on that date and a January 1 effective date would correspond to the contracting period for the Coordinated Care Organizations, as has been done in previous years.

Ø **Topic: Straightforward/Consent Agenda**

Discussion: There was no discussion.

MOTION: To approve the consent agenda as presented. CARRIES 8-0.

Actions:

1) Add 45397 (Laparoscopy, surgical; proctectomy, combined abdominoperineal pull-through procedure (eg, colo-anal anastomosis), with creation of colonic reservoir (eg, J-pouch), with diverting enterostomy, when performed) to line 161 Cancer of colon, rectum, small intestine and anus
2) Add 44310 (Ileostomy or jejunostomy, non-tube) to line 158 Vascular Insufficiency of Intestine
3) Lymphedema, NOS (I89.0) was moved from line 579 LYMPHEDEMA to line 427 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
4) I89.1 (Lymphangitis) was moved from 579 LYMPHEDEMA to 209 SUPERFICIAL ABSCESSES AND CELLULITIS

Ø **Topic: Quality of Evidence Document**

Discussion: Livingston reviewed the documents on quality of evidence and criteria for topic reviewed for VbBS. The subcommittee approved the criteria for topic selection document without changes. On the Quality of Evidence Document, the subcommittee made a few wording changes to the document, clarifying that consistency as well as strength of evidence is important. See Appendix C for the revised text, with meeting edits shown in red text.

Actions: Approved two documents on:

1) Criteria for Topic Review (approved as it appeared in the meeting materials.)

2) Quality of Evidence Statement for the Prioritized List of Health Services. (As shown in Appendix C)

Ø Topic: Treatments for gender dysphoria

Discussion: Smits reviewed the literature on the effectiveness and risks of cross-sex hormone therapy and sex reassignment surgery. Based on poor quality evidence, these treatments are effective at improving quality of life and reducing gender dysphoria symptoms. The high morbidity and mortality of gender dysphoria was reviewed, which includes increased deaths due to suicide, accidents, HIV infection, increase suicide attempts, and IV drug abuse.

Testimony was heard from Dr. Bruce Boston, pediatric endocrinologist at OHSU, from Dr. Megan Bird, OB/GYN at Legacy and Danielle Askini from Basic Rights Oregon. The high rate of suicide attempts (44%) among transgendered persons was noted. In a Belgian study, treatment of gender dysphoria with cross-sex hormones, surgery, or some combination, resulted in an 80% reduction in suicide attempts (from 30% to 5%). Transgender individuals also participate in other high risk activities, such as IV drug use, unprotected sex, etc. Hormone/surgical therapy have been found to reduce these risky behaviors as well. The experts testified that hormones and surgery are safe and effective treatments which are considered medically necessary by the American Congress of OB/GYNs, AAFP, APA, and AMA. When questioned about whether hormone treatment alone without surgical options is effective at reducing suicide attempts and other risky behavior, the experts testified that that was not known. All studies have been done on patients who had access to surgical options as well has hormone therapy. In their expert opinion, offering only cross-sex hormone therapy without surgical options would not be very helpful. Boston noted that transgendered young adults who have received appropriate treatment have been found to be better adjusted than age-matched controls. The experts offered to provide citations to HERC staff for the above referenced studies. Dr. Bird will provide HERC staff with the WPATH guidelines, which are proprietary.

Pollack raised concerns about patients with personality disorders and other psychological/psychiatric problems. He states that if surgical treatment of gender dysphoria is added to the Prioritized List, it must be accompanied by a strict guideline about evaluation and treatment of psychiatric co-morbidities. The experts noted that the major guideline in this area, from WPATH, requires psychological evaluation by both an MD/PhD level clinician and from a master's level clinician.

The subcommittee directed staff to work with experts to look at the mortality reduction (from suicide and risky behaviors such as IV drug use) resulting from treatment of gender dysphoria.

The experts noted to staff that some patients cannot take hormones due to medical contraindications. Any guideline should allow for surgical options without hormonal options due to this fact.

There was discussion about the expected costs of covering cross-sex hormone therapy. It is not known how many transgendered persons are in the Oregon Medicaid program or what the cost of treatments might be. There are also possible cost savings from avoiding suicide attempts, etc. The experts noted that Washington, California, Vermont, and DC Medicaid all cover cross-sex hormone therapy and sex reassignment surgery. The California Department of Insurance has done a study on the costs of this treatment in California and found a minimal increase in the costs to the Medicaid program once these therapies were covered. There is also a study from UCLA and data from San Francisco on costs of coverage. The experts will help HERC staff find this data.

The subcommittee asked the experts if there was a black market in cross-sex hormone therapy and were told that there was a considerable market in the Portland area. Such therapy is not medically supervised, not at recommended dosages, etc. Allowing coverage of cross-sex hormones would reduce this black market.

Livingston expressed concern about the possible costs of fertility preservation. The experts testified that there was very little interest among these patients in fertility preservation.

Actions:

1) HERC staff will work with experts to find data on harm reduction and on costs for addition of cross-sex hormone therapy and sex reassignment surgery.
2) Staff will mock up a separate line for hormone and surgery as treatments for gender dysphoria and suggest prioritization scoring for it. If the scoring results in a line close to the existing line for gender dysphoria (413), then these services will be proposed for addition to the existing line. If not close, the proposal will be to create a separate line on the biennial list tentatively scheduled for April 1, 2017.

Ø **Topic: Applied behavioral analysis for autism spectrum disorder**

Discussion: Livingston reviewed the summary document on ABA therapy for autism spectrum disorder. She noted that staff recently participated in a conference call during which they became aware of potential issues with the current draft due to federal parity rules for mental health care, and asked the subcommittee to defer discussion of the hour and duration limits until the next meeting.

Dr. Larsson, who served as one of three appointed ad hoc experts during the EbGS evaluation of evidence, reviewed the new procedure codes created for ABA. These are temporary codes approved for use after July 1. He said he wasn't sure they added anything over codes currently being used by private payers. He also commented that the hour limits in the draft evaluation are not based on his understanding of the evidence but more on Senate Bill 365 and other factors, as many of the studies included in the source report used more than 25 hours per week of intensive therapy. He also discussed his alternate proposals which have more of a focus on progress evaluation for continued coverage than on limitations on intensity and duration of treatment.
Dodson then invited public comment. Tobi Rates testified first, as the executive director of the Autism Society of Oregon and parent of two children with autism. She expressed appreciation for the recommendations for coverage but also expressed concern about the limits of eight hours per month. She said for her 9 year old, 8 hours per month isn't enough to make a difference in quality of life. She said that EbGS didn't adequately consider the impact on healthy life, and mentioned that Dr. Larsson and Dr. Zuckerman (also an appointed expert) disagreed with the hour limits in the draft evaluation of evidence, and expressed concern about compliance with mental health parity laws. She would prefer to have coverage begin as soon as possible, even if it is with pre-existing codes.
Brenna Legaard also offered comment. She is the mother of a six year old with autism, and said she had to sue an insurance company in order to get coverage, and argued that waiting for the temporary codes to be approved might delay implementation. She said that parents of children with autism are limited in their ability to have jobs due to care demands, and expressed support for more intensive treatment than the current draft recommendations so as to maximize the chance for parents to return to the workforce and participation in the community.

Shane Jackson, a lobbyist from Oregon Association for Behavior Analysis and the Autism Society of Oregon also spoke, saying that the age and hour limits are inconsistent and will cause problems in the future due to some plans having such limits and others that will not due to federal standards. He also said that he didn't believe that the impact of autism on the society and family as well of the individuals.

Coffman addressed the comments about timing of implementation due to coding changes. The language in Senate Bill 365 was based on an expected ICD-10 implementation on October 1, 2014. ICD-10 has been delayed one year, and staff is still assessing the impact of this delay, along with the new temporary codes. The advocates proposed code H2010 as an appropriate code for ABA. Coffman pointed out that this code does not really relate to ABA services. He said the temporary codes more accurately reflect ABA services and would lead to more appropriate reimbursement.

Olson asked whether there are studies about the impact of autism on families. Legaard stated that the evidence evaluation was focused on efficacy of treatment, but that she believes there are studies on the larger impact. Livingston said that the subcommittee included a rating of "low variability" in the values and preferences column of the GRADE table in the evidence evaluation because it assumed that families would want the therapy and that improvements in these behaviors would be important for families. Legaard said that advocates began to doubt that they were being heard because of the limit of 8 hours per month for older children seems inadequate for children with severe behavioral issues, and the single subject research design literature shows effectiveness for these therapies for many children.

Actions:

1) Staff will bring back revised recommendations, including recommendations on self-injurious behavior for children with self injurious behavior.

Ø **Topic: Rehabilitation therapies guideline**

Discussion: Smits reviewed the proposed new rehabilitation therapies guideline. The discussion mainly centered on making the guideline as simple and straightforward as possible. The OHP plans are not finding a need to have specific limits on the number of visits. Taray noted that the wording regarding the need for services, the qualifications of provider, and the need for medical review are very helpful for DMAP and mirror current OHP rules. The subcommittee decided to not specify visit limits and left in wording only specifying medical necessity and review. The line specifying unlimited visits during hospitalization/rehabilitation facility stays was thought to be unnecessary and removed.

Pulmonary rehabilitation was noted to not be included in this guideline. Staff was directed to review whether a guideline should be included regarding pulmonary rehabilitation.

MOTION: To approve the revised guideline as amended. CARRIES 8-0.

Actions:

1) The rehabilitation guideline was modified as shown in Appendix A

Ø **Topic: Guideline revision for treatment of sleep apnea**

Discussion: Livingston reviewed the summary of suggested changes for the treatment of sleep apnea line and guideline. The wording of "covered" was changed to "included on this line" in the guideline, and surgical codes which would be removed from the sleep apnea line to align with the guideline. After

brief discussion, the subcommittee approved the recommendation with slight wording changes to correctly indicate that surgery for sleep apnea is "not included on this line" rather than "not covered."

MOTION: To approve coding changes and the guideline as amended. CARRIES 8-0.

Actions:

1) Remove from line 210 SLEEP APNEA AND NARCOLEPSY
    a. 21193-21199, 21206-21215, 21230, 21235, 30117, 30140, 30520, 42140, 42145, 42160
2) Add to line 646
    a. 21199
3) Advise DMAP to add to the Excluded List
    a. 42140
4) Modify GN 27 as shown in Appendix A

Ø **Topic: Fluoride varnish guideline revision**

Discussion: Livingston introduced a summary document regarding suggested changes to the fluoride varnish guideline. The suggestion was to not allow primary care providers to apply fluoride varnish. Livingston reviewed the evidence that allowing PCPs to apply fluoride varnish reduces dental caries and increases referrals to dentists. Tyack said this is controversial among some dentists but agreed that fluoride varnish application in primary care homes should be covered.

Actions:

1) No changes made to the current guideline

Ø **Topic: Computer aided mammography**

Discussion: Livingston introduced the summary of evidence and recommendations for mammography with computer-aided detection (CAD). The subcommittee discussed adding 77051 (diagnostic mammography with CAD) to the Excluded List as well as 77052 (screening mammography with CAD) due to the lack of evidence of any benefit and the evidence of harm. The proposed diagnostic guideline note was changed to include both diagnostic and screening CAD mammograms and the wording "for breast cancer screening" was removed to reflect the VbBS desire to not cover CAD for any indication. There was some discussion about adding the CAD codes to the new section of the Prioritized List for items reviewed but not placed on the List; however, it was pointed out that the codes would be in the diagnostic guideline and therefore searchable and that the guidelines carried more weight than the new section due to their reference in statute.

MOTION: To approve the coding changes and the amended diagnostic guideline. CARRIES 8-0.

Actions:
1) Recommend to DMAP to remove 77051 and 77052 from the Diagnostic File and place in the Excluded File
2) A new diagnostic guideline was added as shown in Appendix B

Ø Topic: Electronic tumor treatment fields

Discussion: Smits reviewed the summary document. The subcommittee agreed with creation of a new section of the Prioritized List for items reviewed but not included. This section will include those technologies or treatments with CPT or HCPCS codes that could be placed on one or more lines on the List, but which the commission does not find evidence of effectiveness or finds to be a much more costly alternative. The subcommittee did not agree on the proposed title for this section and recommended staff work on a more streamlined name and bring back to the June meeting to discuss.

The subcommittee agreed that electronic tumor treatment fields (ETTF) should not be added to the Prioritized List, but rather added to this new section of reviewed but not included items. There was discussion about how the entry for ETTF should be written. The decision was made to not include wording about ETTF being second line therapy as the VBBS did not want it included at all. Wording about coverage was changed to inclusion. HERC staff was directed to work on the final wording for this topic and bring back to the June meeting.

Actions:
1) Staff will bring back revised wording of the title for the new reviewed but not included on the List section to the June meeting
2) Staff will bring back revised wording on the entry for ETTF to the June meeting

Ø Topic: Electroconvulsive therapy (ECT)

Discussion: Smits reviewed the staff evidence review and recommendations regarding ECT. Pollack noted that Dr. George Keepers, a psychiatrist at OHSU who specializes in ECT, objected to the draft guideline. He requested that Dr. Keepers be approached to give input. Pollack also recommended looking at the American Psychiatric Association guidelines for ECT.

Actions:

1) Staff will work with Drs. Pollack and Keepers to revised the proposed guideline and seek APA or other guidelines for additional input. This topic will be readdressed at the June meeting.

Ø Topic: Hip fractures

Discussion: There was minimal discussion.

MOTION: To approve the changes to placement of hip fractures as presented. CARRIES 8-0.

Actions:

1) Move open hip fracture ICD-9 and ICD-10 codes from line 136 to line 85
    a. ICD-9 820.x (open fracture of neck of femur)
    b. ICD-10 S72.0xxx (open fracture of head or neck of femur)
2) Remove hip fracture repair CPT codes from line 136
    a. 27236 (Open treatment of femoral fracture, proximal end, neck, internal fixation or prosthetic replacement)
    b. 27267 (Closed treatment of femoral fracture, proximal end, head; without manipulation)
    c. 27268 (with manipulation)
3) Rename line 85 FRACTURE OF HIP~~, CLOSED~~

Ø Topic: Transurethral prostatic implants for benign prostatic hypertrophy

Discussion: There was minimal discussion.

MOTION: To approve the placement of the new HCPCS codes as presented. CARRIES 8-0.

Actions:

1) Add HCPCS C9739 (Cystourethroscopy with transprostatic implant; 1 to 3 implants) and C9740 (4 or more implants) to line 331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION

Ø Topic: Lymphedema

Discussion: Smits introduced the summary of a suggested reorganization and rescoring of the lymphedema line. The subcommittee was in agreement that the lymphedema diagnoses be combined on a line with scoring that would place it in the funded region.

The HSC placed the post-mastectomy lymphedema and other lymphedema codes on a line for complications of a procedure. The intention was to cover the lymphedema that resulted as a complication of a surgery, radiation, etc. Taray informed the subcommittee that DMAP is currently interpreting the placement on the complications line as requiring the lymphedema itself to have a complication, such as ulceration, to allow treatment. This is not HSC/HERC intent. HERC desires lymphedema treatment as a preventive service to avoid such complications.

John Beckwith, PT, testified about his experiences working with patients with lymphedema. He noted that many lymphedema patients have lymphedema that does not arise as a complication from surgery, chemotherapy, etc. He also advocated for covering treatment of patients with severe venous insufficiency to prevent ulceration, etc. Venous insufficiency not related to lymphedema is not currently covered.

The subcommittee heard that DMAP determines coverage of DME, as there are decisions about vendor, type of product, etc. which is too much detail for HERC to determine. Pollack requested that this information be placed on the HERC organizational chart.

The subcommittee reiterated that the HERC intends that lymphedema treatment should be covered when the lymphedema has not resulted in any complications such as ulcerations. The HERC intends that appropriate DME be covered for treatment of lymphedema, such as compression sleeves.

Actions:

1) HERC staff to evaluate adding a sentence about DME to the current lymphedema guideline
2) HERC staff to review possible coverage of some types of preventive treatment for venous insufficiency
3) Move the following ICD-9 codes to the lymphedema line and remove from all other lines as part of the current biennial review
    a. 457.0 Postmastectomy lymphedema syndrome
    b. 457.1 Other lymphedema
4) Move the following ICD-10 codes to the lymphedema line and remove from all other lines as part of the current biennial review
    a. Postmastectomy lymphedema (I97.2)
    b. Lymphedema, NOS (I89.0)
5) Move 457.1/I89.1 (lymphangitis) to line 214/209 SUPERFICIAL ABSCESSES AND CELLULITIS and remove from line 598/579 as part of the current biennial review
6) Reprioritize the lymphedema line as shown below as part of the current biennial review

Line XXX
Condition: LYMPHEDEMA
Treatment: MEDICAL THERAPY, OTHER OPERATION ON LYMPH CHANNEL
ICD-9: 457.0-457.9, 757.0
ICD-10: I89.0, I89.8, I89.9, Q82.0
CPT codes: same as current lymphedema line

Scoring
Category : 7
HL: 4
Suffering: 1
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 2
Effectiveness: 3
Need for service: 0.8
Net cost: 3
Score: 288
Approximate line placement: line 470

Ø **Topic: Somatization/factitious disorder line merge**

Discussion: Smits introduced a summary of the Behavioral Health Advisory Panel's (BHAP) recommendation to merge lines 462 FACTITIOUS DISORDERS and 497 SOMATIZATION DISORDER; SOMATOFORM PAIN DISORDER, CONVERSION DISORDER. BHAP had charged staff with devising proposed scoring for this new line. The subcommittee agreed with merging these lines, but had considerable debate on the scoring of this new line. It was noted that line 462 had been given a category score of "6" which includes fatal illnesses, which had resulted in its relatively high priority line placement. This condition is not fatal, and the appropriate category for the combined line is "7." Scores between 0.8 and 1.0 for "need for service" were proposed, with the final decision being 0.9. Net cost was given a 3, because correct treatment of these conditions involves only office visits and should have some cost savings due to reduced ER visits, testing, etc.

MOTION: To approve the new combined line as presented with amended scoring. CARRIES 8-0.

Actions:
1) Merge lines 462 FACTITIOUS DISORDERS and 497 SOMATIZATION DISORDER; SOMATOFORM PAIN DISORDER, CONVERSION DISORDER with line details and scoring as shown below

Line XXX
Condition: SOMATIC SYMPTOMS AND RELATED DISORDERS
Treatment: CONSULTATION
ICD-9: 300.16, 300.19, 300.7-300.9, 301.51, 306.x, 307.8x
ICD-10: F68.1x, F44.x, F45x, F52.5
CPT: from line 462 + 96150-96154
HCPCS: from line 497

Scoring
Category: 7
HL: 2
Suffering: 2
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 0
Effectiveness: 1
Need for service: 0.9
Net cost: 3
Score: 72
Approximate line placement: 556

Ø **Topic: Restructuring of low back pain lines**

Discussion: Smits introduced a summary document outlining a proposed change of the low back pain lines from distinguishing the two lines based on radiculopathy/neurologic symptoms to distinguishing them based on effective vs ineffective treatments. In general, the subcommittee liked the general idea of change to effective/ineffective treatments. However, there was discussion that effective treatments are a "moving target" and therefore would require a large amount of continuous review. There was also concern that some therapies may not be effective for a large population, but might be very effective for an individual.

Susan Bamburger, PT, past president of the OR PT association, gave testimony. She testified that most patients with radicular pain started with non-radicular pain, which was not adequately managed and therefore progressed to radicular pain. Treating the patient earlier in the course of the disease, before radicular symptoms or other complications develop, is more effective. She urged treatments to be chosen that are right for the individual patient rather than best in an RCT. She thought the lines should be distinguished based on signs and symptoms rather than cause of the pain.

Further discussion in the subcommittee included a discussion that surgical care is very much determined by neurological symptoms. Any change in how the List

is structured would have a significant financial impact based on changing surgical indications. Williams requested that the two spinal deformity lines be included in a review of the low back pain lines. Taray suggested also including the dysfunction lines in this review.

There was a sense that a larger review of the back pain lines should be done, and that such a review would take time. It is unlikely to be completed by August to be a part of the current biennial review. However, the new lines could be modifications of the existing lines and therefore be a non-biennial review change.

The subcommittee requested that staff create a task force to review the low back pain lines as well as the spinal deformity lines and come up with a proposal restructuring these lines. The dysfunction lines should be reviewed and some diagnoses and treatments moved to the back pain lines as well. This task force would be charged with determining how to determine when a diagnosis or treatment would be on the covered line. Task force membership should include a physical therapist, an acupuncturist or other alternative medicine practitioner, a spinal surgeon, a primary care provider, a member of the Oregon Pain Management Commission, physical medicine and rehabilitation, and other members as staffs sees fit.

Actions:

1) HERC staff will convene a taskforce on low back pain as outlined above

Ø **Topic: Miscellaneous Conditions with No or Minimally Effective Treatments or No Treatment Necessary**

Discussion: There was minimal discussion.

MOTION: To approve the new line as presented. CARRIES 8-0.

Actions:

1) Rename line 669 GASTROINTESTINAL CONDITIONS ~~AND OTHER MISCELLANEOUS CONDITIONS~~ WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
2) Create a new line for miscellaneous conditions with no treatment necessary or no effective treatment with scoring as shown below
    a. Remove all included ICD-9 and ICD-10 diagnoses from their current lines
3) Move the following ICD-9 diagnoses from current lines to line 684 ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    a. 256.0 (Hyperestrogenism), 272.6 (Lipodystrophy), 272.8 (Other disorders of lipoid metabolism)

Line XXX
Condition: MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
Treatment: EVALUATION
ICD-9: 744.5, 744.8x and 744.9, 748.1, 754.0, 994.5
ICD10: E66.3, E67.2, E67.8, Q18.3, Q18.4, Q18.5, Q18.6, Q18.7, Q18.8, Q18.9, Q30.x, Q67.x, T73.3
CPT: 98966-98969,99051,99060,99070,99078,99201-99215,99281-99285, 99341-99355,99358-99378,99381-99404,99408-99412,99429-99449, 99487-99496,99605-99607
HCPCS: G0396,G0397,G0463

Scoring
Category: 9
HL: 0
Suffering: 0
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 0
Effectiveness: 0
Need for service: 0
Net cost: 0
Score: 0
Line placement: 670 (last line of the list)

Ø **Topic: Injuries to blood vessels of the neck**

Discussion: There was discussion about whether a new line was needed for injuries to blood vessels of the neck. The subcommittee decided to add these diagnoses to the existing injury to major blood vessels of the extremities line and change the line title to include the neck. This was thought to be a simpler solution and the line priority appropriate for the seriousness of these injuries.

MOTION: To approve the movement of the injury to blood vessel in the neck codes to line 82. CARRIES 8-0.

Actions:
1) Move ICD-9 (900.xx) and ICD-10 (S15.xxx) codes for injuries to the blood vessels of the neck from Line 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME to line 82 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES
2) Move the CPT codes for repair of neck vessels from line 135 to line 82
    a. 35201 Repair blood vessel, direct; neck
    b. 35231 Repair blood vessel with vein graft; neck

c. 37615 Ligation, major artery (eg, post-traumatic, rupture); neck
d. 37565 Ligation, internal jugular vein

3) Rename line 82 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES AND NECK

Ø **Public Comment:**

No additional public comment was received.

Ø **Next Steps**

Issues for next meeting:

- Continued discussion of treatments for gender dysphoria:
  - Cross-sex hormone therapy
  - Sex reassignment surgery
- Continued discussion of ABA therapy for autism spectrum disorders
- Hearing loss issues
  - Biennial review deletion of audiant bone conductor for conductive hearing loss line
  - Unilateral hearing loss
  - Bone anchored hearing aids
- Physical therapy for urinary incontinence
- Electronic tumor treatment fields
- Electroconvulsive therapy (ECT) guideline
- Potential new guidelines on:
  - Treatment of hepatitis C
- Potential revisions to existing guidelines on:
  - Bariatric surgery (clarification)
  - Lymphedema
- Treatments for venous insufficiency
- Microwave thermoplasty for benign prostatic hypertrophy
- Physical therapy for urinary incontinence
- Pairing of diagnoses with osteopathic manipulation

Ø **Next meeting:**

June 12, 2014 at Meridian Park Hospital Health Education Center, Conference Room 117B&C in Tualatin, OR

Ø **Adjournment**

The meeting was adjourned at 1:40 pm.

Appendix A

Revised Guidelines

GUIDELINE NOTE 6, REHABILITATIVE THERAPIES

Lines 37,50-52,64,74-76,78,80,85,89,90,94,95,98-101,108,109,115,116,122,129,139,141-143,145,146,158,161,167,179,184,185,189,190,192,194,195,201,202,208,209,216,226,237,239,270,271,273,274,279,288,289,293,297,302,304,307-309,318,336,342,349,350,363,367,369,375,376,378,382,384,385,387,400,406,407,434,441,443,448,455,467,478,489,493,507,516,535,549,562,580,597,619,638

Physical, occupational and speech therapy, and cardiac and vascular rehabilitation are only included on these lines when the following criteria are met:

1) therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide physical, occupational, or speech therapy,
2) there is objective, measurable documentation of progress toward the therapy plan of care goals and objectives,
3) the therapy plan of care requires the skills of a therapist, and
4) the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

~~Physical, occupational and speech therapy, and cardiac and vascular rehabilitation, are covered for diagnoses paired with the respective CPT codes, depending on medical appropriateness, for up to 3 months immediately following stabilization from an acute event.~~

~~Following the 3 month stabilization after an acute event, or, in the absence of an acute event, the following number of combined physical and occupational therapy visits are allowed per year, depending on medical appropriateness:~~

~~• Age < 8: 24~~
~~• Age 8-12: 12~~
~~• Age > 12: 2~~

~~And the following number of speech therapy visits are allowed per year, depending on medical appropriateness (with the exception of swallowing disorders, for which limits do not apply):~~

~~• Age < 8: 24~~
~~• Age 8-12: 12~~
~~• Age > 12: 2~~

~~Whenever there is a change in status, regardless of age, such as surgery, botox injection, rapid growth, an acute exacerbation or for evaluation/training for an assistive communication device, the following additional visits are allowed:~~

~~• 6 visits of speech therapy and/or~~
~~• 6 visits of physical or occupational therapy~~

Appendix A

~~No limits apply while in a skilled nursing facility for the primary purpose of rehabilitation, an inpatient hospital or an inpatient rehabilitation unit.~~

GUIDELINE NOTE 27, TREATMENT OF SLEEP APNEA IN ADULTS

Line 210

CPAP is covered initially when all of the following conditions are met:

- 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
  - excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score>10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
  - documented hypertension, or
  - ischemic heart disease, or
  - history of stroke;
- Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
- Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30 day period.

Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.

Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Tonsillectomy and adenoidectomy codes are included on this line only for children who meet criteria according to Guideline Note 118 OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT IN CHILDREN.

Appendix B

New Guidelines

DIAGNOSTIC GUIDELINE DXX COMPUTER-AIDED MAMMOGRAPHY

Computer-aided mammography (CPT code 77051 and 77052) is not a covered service.

Appendix C

Health Evidence Review Commission

Quality of Evidence Statement

HERC relies heavily on high quality evidence and evidence-based guidelines in making prioritization decisions.

The following source list illustrates how HERC and the Value-based Benefits Subcommittee (VbBS) view various types of evidence for prioritization decisions. The existence of evidence in the form of a high-quality study design does not necessarily mean that the overall evidence on that topic will be considered high quality. For instance, a high quality systematic review might find that the available studies have significant potential for bias and may conclude there is a low strength of evidence or insufficient evidence to support an intervention.

Lower quality evidence may sometimes be considered in situations where higher quality evidence is difficult to obtain (for example, in rare clinical conditions).

The commission ~~also~~ includes other factors into its decision making process, such as harms, treatment alternatives, health equity and the needs of specific subgroups when relevant data exists.
HERC may consider various factors in evaluating a particular study, including:

- Potential for bias
- Clinical significance of outcomes studied
- Strength and consistency of evidence, not just study quality
- Study relevance based on population and health system characteristics
- Conflicts of interests of the authors

The following sources generally produce high quality evidence and are preferred by HERC:

- Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/
- Blue Cross Blue Shield Technology Evaluation Center (TEC) http://www.bcbs.com/blueresources/tec/
- British Medical Journal (BMJ) Clinical Evidence http://www.clinicalevidence.com
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA) http://www.cadth.ca/index.php/en/hta
- Cochrane Database of Systematic Reviews http://www2.cochrane.org/reviews/
- Evidence-Based Practice Centers (EPC) www.ahcpr.gov/clinic/epc
- Health Technology Assessment Programme - United Kingdom http://www.hta.nhsweb.nhs.uk/ProjectData
- National Institute for Clinical Excellence (NICE) - United Kingdom http://guidance.nice.org.uk/
- Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/guidelines/index.html
- University of York http://www.york.ac.uk/inst/crd/

The following types of study designs can be considered high quality and are preferred by HERC:

- Systematic reviews of randomized controlled trials

Appendix C

- Systematic reviews of prospective cohort studies
- Evidence-based guidelines from trusted sources

The following types of study designs/documents can be considered lower quality and are often reviewed by HERC:

- Guidelines issued by professional societies and advocacy organizations (e.g. American Heart Association)
- Coverage decisions by private health plans (e.g. Aetna)
- Well-conducted, peer-reviewed individual studies (experimental or observational)

The following types of evidence can be considered very low quality and are seldom reviewed by HERC:

- Case reports, case series
- Unpublished studies (posters, abstracts, presentations, non-peer reviewed articles)
- Individual studies that are poorly conducted, do not appear in peer-reviewed journals, are inferior in design or quality to other relevant literature, or duplicate information in other materials under review by the Commission

Section 2.0

New Discussion Items

Conductive Hearing Loss Treatment with Audient Bone Conductors

Question: Should the line for audient bone conductors as treatment for conductive hearing loss be removed from the Prioritized List?

Question source: HERC staff

Issue: [note: lines refer to the October 1, 2014 Prioritized List]. Line 570 CONDUCTIVE HEARING LOSS; Treatment: AUDIANT BONE CONDUCTORS has no unique diagnosis or treatment codes other than the CPT code for insertion of audient bone conductors. This line is contained with no changes on the ICD-10 List.

Audiant (Medtronic Xomed, Inc., Jacksonville, FL) Bone Conductor, also known as the temporal bone stimulator, is an FDA-approved implanted device with an external processor that uses transcutaneous inductive electromagnetic energy to cause vibration of an implanted titanium magnet screwed into the temporal bone. This device is no longer marketed and is not available.

In April, 2008, the HSC removed the audient bone conductor placement CPT code from 2 lines on the List as this technology was noted to not be in use. However, these CPT codes still appear on the List.

Codes:

69710 Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone (427 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT, 570)

69711 Removal or repair of electromagnetic bone conduction hearing device in temporal bone (290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT, 427, 570)

Conductive hearing loss ICD-9/10 codes appear on lines 317 HEARING LOSS - AGE 5 OR UNDER; Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS, 450 HEARING LOSS - OVER AGE OF FIVE; Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS, and 570 CONDUCTIVE HEARING LOSS; Treatment: AUDIANT BONE CONDUCTORS.

The only other treatments on line 570 are hearing testing and other treatments also found on the other hearing loss lines.

HERC staff recommendations:

1) Delete line 570 CONDUCTIVE HEARING LOSS Treatment: AUDIANT BONE CONDUCTORS from the Prioritized List
    a. No need to move any diagnosis or treatment codes from line 570 as all relevant codes appear elsewhere on the List
2) Remove CPT 69710 (Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone) from line 427 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
3) Keep CPT 69711 (Removal or repair of electromagnetic bone conduction hearing device in temporal bone) on line 427, remove from line 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
4) Add the following entry to the items reviewed but not on the Prioritized List as shown below

HERC Reviews of Health Technology for Items Not Placed on the Prioritized List

AUDIANT BONE CONDUCTORS

Most recent review date: April, 2014

Audiant bone conductor therapy (CPT 69710) has been found to be less effective that other forms of treatment for conductive hearing loss. HERC recommends that audient bone conductors not be used. See VBBS/HERC minutes from 5/8/14 for details [link].

Treatment of Unilateral Hearing Loss

Question: Should treatment of unilateral hearing loss be covered? Should such coverage be for children, adults, or both?

Question source: OHP Medical Directors

Issue: currently, there are no guidelines or other guidance in the Prioritized List for the health plans on whether unilateral hearing loss is covered, or types of treatment are covered.

From John Sattenpiel, OHP Medical Director

> Actually the important question is coverage for unilateral hearing loss. There is some soft evidence of limited benefit but on my review there is also controversy regarding whether the magnitude of the benefit is significant and the published guidance is mixed with some recommending use of hearing aids and others indicating not to do so. We really need HERC guidance about whether or not correction of unilateral hearing loss in children and/or adults is intended to be covered.

Current Prioritized List information

Hearing loss is covered on the following lines:

> 283 SENSORINEURAL HEARING LOSS - AGE 5 OR UNDER; Treatment: COCHLEAR IMPLANT
> 317 HEARING LOSS - AGE 5 OR UNDER; Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS
> 423 SENSORINEURAL HEARING LOSS - OVER AGE OF FIVE; Treatment: COCHLEAR IMPLANT
> 450 HEARING LOSS - OVER AGE OF FIVE; Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS
> ~~570 CONDUCTIVE HEARING LOSS; Treatment: AUDIANT BONE CONDUCTORS~~

Per GUIDELINE NOTE 49, COCHLEAR IMPLANTS, OVER AGE 5, cochlear implants are only covered for bilateral hearing loss.

Evidence:

1) **Cincinnati Children's Hospital 2011,** best evidence recommendations for treatment of single sided deafness in children
    a. School age children (ages 7-18 years) with single sided deafness
    b. A review of the current literature suggests that amplification versus no amplification improves quality of life and therefore offered as a part of care. Two of the most commonly reported challenges for patients with SSD are the ability to localize sound and speech understanding in noise. Therefore, most research studies have been designed to measure benefit

with amplification in these two conditions, and failed to consistently show improvement in both. Quality of life measures for adults, however, have consistently shown benefit in the following conditions: listening in background noise, ease of communication and listening in reverberant conditions. The studies evaluating children with SSD as well as studies involving children with unilateral hearing loss (UHL), suggest that functional outcome measures such as the CHILD, LIFE and a questionnaire by McKay (2002), indicate improvement in quality of life with amplification.

c. It is recommended that for children with single sided deafness (SSD) amplification be offered

2) **Cincinnati Children's Hospital 2009,** best evidence recommendations for management of single sided deafness in children
   a. It is recommended that school-aged children with severe to profound unilateral sensorinerual hearing loss (USNHL) be fit with a contralateral routing of signal (CROS) system as the first line of amplification technology
   b. It is recommended that children with mild to moderate sensorineural UHL be fit with a hearing aid (FM ready) as the first line intervention and with a CROS type system as a second line treatment
3) **Kamal 2012**, review of cochlear implants for unilateral hearing loss
   a. Conclusion: Although single-sided deafness is not a currently approved indication for cochlear implantation, limited investigational studies to date have demonstrated patient improvement in both sound localization and speech perception.
4) **Son and Choo 2012**, review of treatment for single sided deafness
   a. Found treatment reasonable, recommended starting with a CROS type device. If not satisfactory, a BAHA is indicated

<u>Other policies</u>

1) Aetna 2014
   a. Covers treatment of unilateral conductive or mixed conductive and sensorineural hearing loss

2) BCBS 2012
   a. Covers treatment of unilateral conductive or mixed (conductive and sensorineural) hearing loss

Treatment of Unilateral Hearing Loss

HERC staff recommendation

1) Adopt the following new guideline for lines 317 and 450

GUIDELINE NOTE XXX TREATMENT OF UNILATERAL HEARING LOSS

Lines 317, 450

Unilateral hearing loss treatment is covered with the following conditions:

1) For mild to moderate sensorineural unilateral hearing loss, first line intervention should be a conventional hearing aid, with second line therapy being contralateral routing of signal (CROS) system
2) For severe to profound unilateral sensorinerual hearing loss, first line therapy should be a contralateral routing of signal (CROS) system with second line therapy being a bone anchored hearing aid (BAHA)
3) Cochlear implants are not covered for unilateral hearing loss per guideline note 49 COCHLEAR IMPLANTS, OVER AGE 5

Best Evidence Statement (BESt)

Date published/posted 6/20/11

Topic: Effects of Amplification on Quality of Life Among School Age Children with Single Sided Deafness

Clinical Question

P: Among school age children with single sided deafness
I: does amplification bone conduction hearing aids
C: versus no amplification
O: improve quality of life (QoL)

Definitions:

Amplification:
For the purpose of this study, amplification is defined as: Contralateral routing of Signal (CROS), bone anchored hearing aid (BAHA), bone conduction hearing aids (Transcranial aid).

.

Quality of Life:
For the purpose of this project, QoL is defined as the core dimensions of); physical functioning, emotional functioning, social functioning, and school functioning.

Other important indicators of QoL in the pediatric population with SSD include hearing in noise, localization, ease of listening and communicating, communication intent and behavior, nature of interpersonal relationships and involvement in recreational activities.

Target Population

- School age children (ages 7-18 years) with single sided deafness.
- Children with additional learning disabilities are excluded.

Recommendation

It is recommended that for children with single sided deafness (SSD) amplification be offered *(Hol, 2010 [3b], Christensen, 2010 [4a], House 2010 [3a]).*
Note 1: *Selected educational and family outcomes are important to monitor when amplification is used or if a decision is made not to provide amplification (McKay 2010 [5a]).*
Note 2: *Utilize Quality of Life measurements with any child identified with SSD and their families (Borton 2010 [3a]).*
Note 3*: Educate parents/families and the child on the impact of single sided deafness regarding the potential effects of the hearing loss, current amplification options, costs, and realistic expectations about the devices may increase their ability to make informed an decision regarding interventions (Borton, 2010 [3a], McKay 2010 [5a]).*

Discussion/summary of evidence

A review of the current literature suggests that amplification versus no amplification improves quality of life and therefore offered as a part of care *(House, 2010 [4b], Hol, 2009 [3b], Yuen, 2009 [3a], Linstrom 2009 [3a], Christensen, 2010, [4a])*. Two of the most commonly reported challenges for patients with SSD are the ability to localize sound and speech understanding in noise *(Bess, 1986 [5a])*. Therefore, most research studies have been designed to measure benefit with amplification in these two conditions, and failed to consistently show improvement in both *(Hol, 2009 [3b], Hol, 2005 [3a], Linstrom, 2009 [3a])*. Quality of life measures for adults, however, have consistently shown benefit in the following conditions: listening in background noise, ease of communication and listening in reverberant condition*s (House, 2010 [4b], Hol, 2009 [3b], Yuen, 2009 [3a], Newman, 2008 [3b], Linstrom, 2009 [3a])*. The studies evaluating children with SSD *(Christensen, 2010 [4a], Christensen, 2008, [4b])* as well as studies involving children with unilateral hearing loss (UHL), *(Borton, 2008 [3a], Wendorf, 2010, [3a])* suggest that functional outcome measures such as the CHILD, LIFE and a questionnaire by McKay (2002), indicate improvement in quality of life with amplification. These findings suggest that more consistent test protocols utilizing quality of life measures are necessary to gather information on the effects of amplification for children with SSD.

Health Benefits, Side Effects and Risks

The primary risk of amplification is dependent upon the amplification device chosen. Amplification options are divided into surgical and nonsurgical options.

The most common surgical option is the Bone Anchored Hearing Aid (BAHA) which includes the general risks involved in surgical procedures, such as anesthesia and infection as well as the potential failure of the device to integrate with the bone. Another consideration is the high cost of the surgical procedure compared to the outcome benefits. The appearance of the device has also been a concern reported by some patients.

The nonsurgical options include cross routing of signal hearing aids (CROS aids) and bone conduction hearing aids (the TransEar and Transcranial CROS in-the-ear hearing aids). The cost of the device is a consideration as most hearing aids are not covered by insurance companies. The appearance of these devices has also been expressed as a concern by some patients and their parents.

Common to all amplification devices is the time and effort to manage the hearing devices and the possibility that some children may have difficulty appropriately managing their devices, depending on their dexterity and developmental skills.

References (evidence grade in *[ ]; **see Table of Evidence Levels following references***)

Christensen, AuD, L., Richter, MD, G. T., & Dornhoffer, MD, J. L. (2010). Update on Bone-Anchored Hearing Aids. *Arch Otolaryngol Head Neck Surg*, 175-177.*[4a]*

Bess, F.H. (1986). An Introduction to Unilateral Sensorineural Hearing Loss in Children. *Ear and Hearing,* 3-13.*[5a]*

Borton, S. A., Mauze, E., & Lieu, J. E. (2010). Quality of Life in Children Wiith Unilateral Hearing Loss: A Pilot Studey. *American Journal of Audiology*, 61-72.*[3a]*

Christensen, L., & Dornhoffer, J. L. (2008). Bone-Anchored Hearing Aids for Unilateral Haering Loss in Teenagers. *Otology & Neurology*, 1120-1122.*[4b]*

Hol, M. K., & Kunst, S. J. (2010, June). Pilot study on the effectiveness of the conventional CROS, the transcranial CROS and the BAHA transcranial CROS in adults with unilateral inner ear deafness. *European Archives of Oto-Rhino-Laryngology*, 889–896.*[3b]*

House, MD, J. W., Kutz, Jr. MD, J. W., Chung, MA, J., & Fisher, PhD, L. M. (2010). Bone-Anchored Hearing Aid Subjective Benefit for Unilateral Deafness. *The Laryngoscope*, 601-607.*[4b]*

Lin, L.-M., Bowditch, S., Anderson, M. J., May, B., Cox, K. M., & Niparko, J. K. (2006). Amplification in the Rehabilitation of Unilateral Deafness: Speech in Noise and Directional Hearing Effects with Bone-Anchored Hearing and Contralateral Routing of Signal Amplification. *Otology & Neurotology*, 172-182.*[3b]*

Linstrom, MD, C. J., Silverman, PhD, MPH, C. A., & Yu, PhD, G.-P. (2009). Efficacy of the Bone-Anchored Hearing Aid for Single-Sided Deafness. *The Laryngoscope*, 713-720.*[3a]*

Martin, T.P,C., Lowther, R., Cooper, H.,, Irving, R., Reid, A., & Proops, D. (2010). The bone-anchored hearing aid in the rehabilitation of single-sided deafness: experience with 58 patients. *Clin. Otolaryngol*, 284–290.*[3a]*

Myrthe K. S. Hol, Hol, M. K., Bosman, A. J., Ad F. M. Snik,, Emmanuel A. M. Mylanus,, Mylanus, E. A., et al. (2005). Bone-Anchored Hearing Aids in Unilateral Inner Ear Deafness: An Evaluation of Audiometric and patient Outcome Measurements. *Otology & Neurotology*, 999–1006.*[3a]*

Newman, C. W., Sandridge, S. A., & Wodzisz, L. M. (2008). Longitudinal Benefit From and Satisfaction With the Baha System for Patients with Acquired Unialteral Sensorinueral Hearing Loss. *Otology & Neurotology*, 1123-1131.*[3b]*

Sammath, PhD, C. A., & Cire, AuD, G. (2009, April). Effectiveness in Treating Single-Sided Deafness with the Baha System. *Hearing Review*.*[5a]*

Schroder, S. A., Tomaas Ravn,, Ravn, T., Per Bonding, & Bonding, P. (2010). BAHA in Single-Sided Deafness: Patient Compliance. *Otology & Neurotology*, 404-408.*[[3b]*

Wazen, MD, J. J., Ghossaini, MD, S. N., Spitzer, PhD, J. B., & Kuller, MS, M. (2005). Localization by unilateral BAHA users. *Otolaryngology–Head and Neck Surgery*, 928-932.*[3b]*

Wazen, MD, J. J., Spitzer, PhD, J. B., Ghossani, MD, S. N., Fayad, MD, J. N., Niparko, MD, J. K., Cox, MS, CCC-A, K., et al. (2003). Transcranial contralateralcochlear stimulation in unilateral deafness. *Otolaryngology - Head and Neck Surgery*, 248-254.*[3b]*

Wazen, MD, J. J., Spitzer, PhD, J., Ghossaini, MD, S. N., Kacker, MD, A., & Zschommler, A. (2001). Results of the Bone-Anchored Hearing Aid in Unilateral Hearing Loss. *The Laryngoscope*, 955-958.*[3b]*

Yuen, Yuen, MBBS, MRCS, DOHNS, H.-W., Bodmer, MD, PhD, D., Smilsky, MclSci, K., Nedzelski, MD, FRCSC, J. M., & Chen, MD, FRCSC, J. M. (2009). Management of single-sided deafness with the bone-anchored hearing aid. *Otolaryngolgoy-Head and Neck Surgery*, 16-23.*[3a]*

Note: Full tables of evidence grading system available in separate document:

- Grading a Body of Evidence to Answer a Clinical Question
- Judging the Strength of a Recommendation (abbreviated table below)

Table of Evidence Levels (see note above)

Quality level	***Definition***
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5 or 5a or 5b	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

Strength	***Definition***
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient *(direct benefit)*
4. Burden to patient of adherence to recommendation *(cost, hassle, discomfort, pain, motivation, ability to adhere, time)*
5. Cost-effectiveness to healthcare system *(balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis)*
6. Directness *(the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome])*
7. Impact on morbidity/mortality or quality of life

Background Information

Children identified with single sided deafness (SSD) are frequently not offered amplification due to limited treatment options and unknown benefits *(Kiese-Himmiel, C., 2002[4a], McKay 2008 [4a])*. The difficulties children experience with unilateral hearing loss (UHL) are described in the literature but there is limited evidence to support the benefit of amplification for SSD, especially with the pediatric population. Current amplification options are inconsistently offered by audiologists *(McKay, 2008 [5a], McKay 2010 [5a])*. This project was developed to discover the evidence around the quality of life benefits for children with SSD fit with amplification.

Supporting information

Group/team members

Team Leader: Lori Garland, M.S, Pediatric Audiologist II, Division of Audiology, Cincinnati Children's Hospital Medical Center
Support Personnel: Barbara K. Giambra, MS, RN, CPNP, Center for Professional Excellence/Research and Evidence-based Practice, Cincinnati Children's Hospital Medical Center

Search strategy

Databases: Ovid Medline, PubMed, Google Scholar and hand search.
Keywords: single sided deafness, unilateral hearing loss, unilateral deafness, amplification, quality of life, treatment, outcomes, guidelines
Limits: English language, all dates included
Retrieved: July 29, 2010 – November 22, 2010

Notification of CCHMC at HPCEInfo@cchmc.org for any BESt adopted, adapted, implemented or hyperlinked by the organization is appreciated.

For more information about CCHMC Best Evidence Statements and the development process contact .the Center for Professional Excellence/Research and Evidence-based Practice office at ***CPE-EBP-Group@cchmc.org*** .

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Reviewed against quality criteria by two independent reviewers

Best Evidence Statement (BESt)

Date published/posted: August 20, 2009

Audiologic management for children with permanent unilateral sensorineural hearing loss

Clinical Question

Population/Problem: In school-age children with either severe to profound unilateral sensorineural hearing loss (SNHL) or mild to moderately severe unilateral SNHL

Intervention: does amplification (i.e. digital hearing aid (HA), Frequency Modulation (FM) system, contralateral routing of signal (CROS) link aid, etc)

Comparison: compared to no amplification

Outcome: improve educational or functional performance?

Target Population

Inclusion: School-age children with any degree of unilateral SNHL

Exclusion: Children with conductive hearing loss

Recommendations

In all children with unilateral SNHL:

1. It is recommended managing providers discuss the potential impact of unilateral hearing loss (UHL) with the child and family to help them understand potential gains, realistic goals, costs, and physical requirements of amplification so they can make an educated decision regarding interventions *(Kenworthy 1990 [3b], McKay 2002 [4b], Updike 1994 [4b], Local Consensus [5])*. See Appendix 1: Tips for Children with Unilateral Hearing Loss.

   Note 1: Be cognizant of cost, which can be an issue in providing a HA or FM system. Most insurance companies do not cover HAs or other amplification devices, nor do they pay for FM systems as covered benefits and many schools do not uniformly provide FM systems for children with UHL *(Local Consensus [5])*. The Bureau with Medical Handicaps covers hearing aids for UHL so if families qualify for Ohio's Bureau of Children with Medical Handicaps (Title V funding), this program will provide coverage for hearing aids for unilateral hearing loss *(Local Consensus [5])*.

   Note 2: Cincinnati Children's Hospital Medical Center (CCHMC) Division of Audiology has a loaner bank for hearing aids and FM systems. Families can borrow a hearing aid or FM system for a period of time *(McKay 2005 [5b])*. The Ohio School for the Deaf has an FM loaner bank for school use. This is directly accessed by schools and the equipment can be borrowed for a 3 month period. These systems can provide an opportunity to have a trial period of amplification/FM system prior to paying for the technology outright *(Local Consensus [5])*.

2. It is recommended, whether or not amplification is provided, that the child and care team (family, health care professionals, clinicians and school personnel) consider monitoring the impact on functional, educational, and behavioral performance as well as academic performance and behavior (family selected outcomes) in the classroom to guide care decisions *(Lieu 2004 [1a], McKay 2008 [5], Local Consensus [5], McKay 2005 [5b])*.

In children with severe to profound unilateral SNHL:

3. It is recommended that school-aged children with severe to profound unilateral sensorinerual hearing loss (USNHL) be fit with an FM system as the first line of amplification technology *(Kenworthy 1990 [3b], Updike 1994 [4b])*. Select an FM system with the most open fit to decrease occlusion in the good ear *(Kopun 1992 [4b])*.

4. It is recommended that provision of a HA in children with severe-profound UHL be on a case-by-case basis *(Kiese-Himmel 2002 [4b], McKay 2002 [4b])*.

   Note 1: Evaluating speech discrimination and speech in noise can provide additional information to guide decision-making *(Updike 1994 [4b], McKay 2005 [5b])*.

   Note 2: If a child has not had success with other amplification interventions, the CROS hearing aid may be considered, though its use has not been wide-spread *(Kenworthy 1990 [3b], Shapiro 1977 [4b])*.

Mild to Moderate Sensorineural UHL:

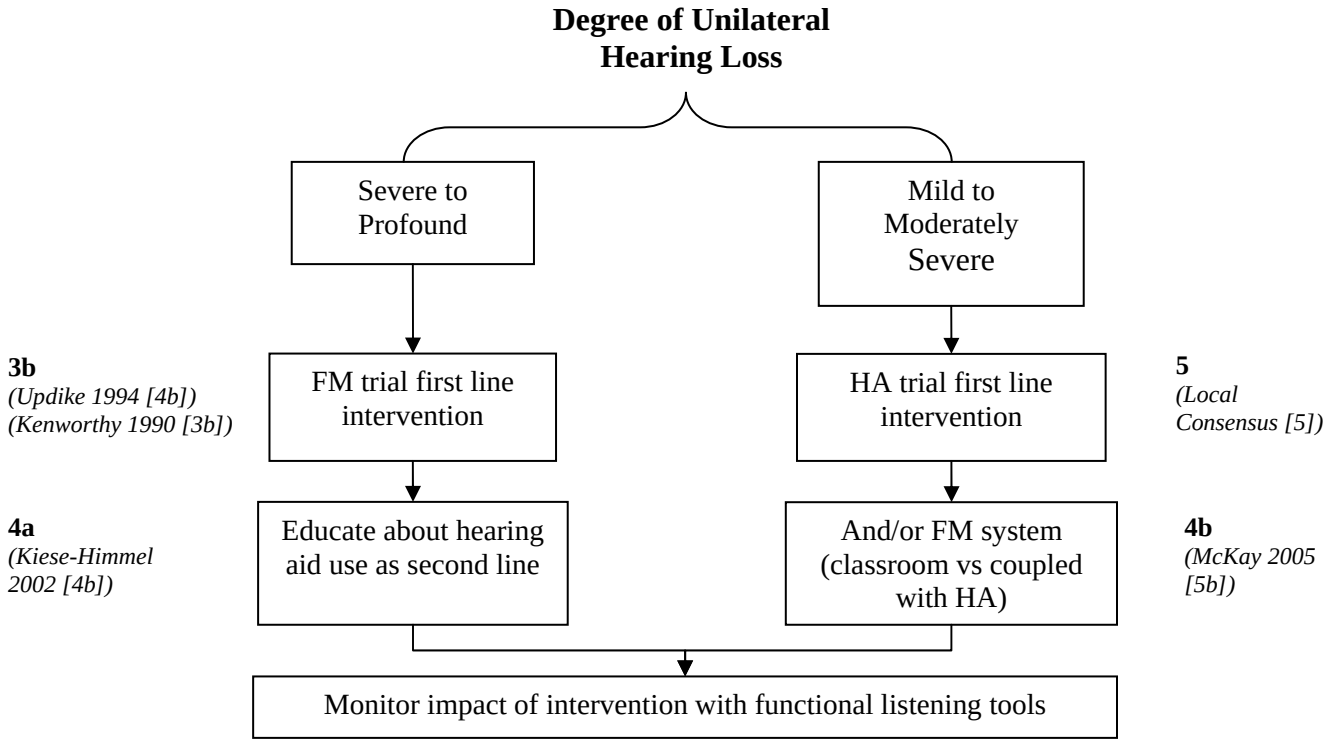
5. It is recommended that children with mild to moderate sensorineural UHL be fit with a hearing aid (FM ready) as the first line intervention *(Kenworthy 1990 [3b], McKay 2002 [4b], Shapiro 1977 [4b], McKay 2005 [5b])*.

   Note 1: There may be theoretical harm in noise-induced hearing loss with amplification in the fitting and monitoring of a HA *(McKay 2008 [5])*.

   Note 2: A non-FM ready smaller HA might be appropriate for a child who does not want a visible HA *(McKay 2008 [5])*.

6. It is recommended provision of an FM system with or without a hearing aid be discussed with the family *(McKay 2002 [4b], Local Consensus [5])*.

   Note: A theoretical risk of an FM system is the loss of access to incidental information and learning. An FM system is most appropriate for use in an educational setting *(Lieu 2004 [1a])*.



FM = frequency modulation system; HA = hearing aid

Discussion/summary of evidence

The quality of the body of evidence regarding school age children with unilateral hearing loss is moderate and limited in guiding interventions and evaluating performance because of the small number of studies, the sample sizes within those studies and the varying amplification systems. See Appendix 2. None of the studies evaluated the impact of amplification on educational or functional outcomes. Therefore, recommendations are based primarily on local clinicians who have come to consensus, but also limited studies describing difficulties children with unilateral hearing loss experience, studies which use clinical settings simulating real life situations such as classrooms with background noise, and survey results from families of patients who have accepted amplification and noted changes in day to day

functioning. It is important to monitor both the effectiveness and potential problems associated with children who choose amplification and children who do not decide to pursue amplification and/or FM systems *(Lieu 2004 [1a], Palmer 2005 [1b], Kenworthy 1990 [3b], Kiese-Himmel 2002 [4b], McKay 2002 [4b], Updike 1994 [4b], Kopun 1992 [4b], Shapiro 1977 [4b], Local Consensus [5], McKay 2005 [5b])*.

Health Benefits, Side Effects and Risks

The primary risk of amplification is in the potential for over-amplification and subsequent damage to existing hair cell function, causing a progression of hearing loss. Basing amplification decisions on behavioral audiometry, having a child who is cooperative and results that are of high reliability will decrease the likelihood of over amplification. Current hearing aid technologies are equipped with loudness controls which help prevent over amplification *(McKay 2008 [5])*.

Negative effects of amplification and/or FM systems include time and effort to manage the hearing devices, cost to the family and potential embarrassment for the child by having attention drawn to their disability. Some children are bothered by wearing a device that makes them look different and therefore may not "buy in" to consistently wearing the amplification device. When using an FM system, although the child can hear what the person using the microphone is saying more clearly, discussion and incidental information from those not using the microphone may be missed, misunderstood or misheard *(Kopun 1992 [4b], Stein 1983 [4b])*.

References/citations (evidence grade in *[ ]; **see Table of Evidence Levels following references***)

Note: When using the electronic version of this document, ☜ indicates a hyperlink to the PubMed abstract. A hyperlink following this symbol goes to the article PDF when the user is within the CCHMC network.

1. **Bess, F. H.; Dodd-Murphy, J.; and Parker, R. A.:** Children with minimal sensorineural hearing loss: prevalence, educational performance, and functional status. *Ear & Hearing*, 19(5): 339-54, 1998, *[4a]* _____ ☜.
2. **Bess, F. H., and Tharpe, A. M.:** Unilateral hearing impairment in children. *Pediatrics*, 74(2): 206-16, 1984, *[4b]* _____ ☜ _____.
3. **Bess, F. H.; Tharpe, A. M.; and Gibler, A. M.:** Auditory performance of children with unilateral sensorineural hearing loss. *Ear Hear*, 7(1): 20-6, 1986, *[4b]* _____ ☜ _____.
4. **Bovo, R.; Martini, A.; Agnoletto, M.; Beghi, A.; Carmignoto, D.; Milani, M.; and Zangaglia, A. M.:** Auditory and academic performance of children with unilateral hearing loss. *Scand Audiol Suppl*, 30: 71-4, 1988, *[4a]* _____ ☜ _____.
5. **CDC:** Annual Early Hearing Detection & Intervention (EHDI) Program Data, 2006. Accessed Mar 2, 2009 from _____and _____ ☜ *[5]*.
6. **Culbertson, J. L., and Gilbert, L. E.:** Children with unilateral sensorineural hearing loss: cognitive, academic, and social development. *Ear Hear*, 7(1): 38-42, 1986, *[4b]* _____ ☜ _____.
7. **English, K., and Church, G.:** Unilateral Hearing Loss in Children: An Update for the 1990s. *Lang Speech Hear Serv Sch* 30(1): 26-30, 1999, *[4a]* _____ ☜ _____.
8. **Flexer, C.; Richards, C.; Buie, C.; and Brandy, W.:** Making the grade with amplification in classrooms. *Hearing Instruments*, 45: 24-26, 1994, *[3b]* ☜ _____.
9. **Hartvig Jensen, J.; Johansen, P. A.; and Borre, S.:** Unilateral sensorineural hearing loss in children and auditory performance with respect to right/left ear differences. *British Journal of Audiology*, 23(3): 207-13, 1989, *[4b]* ☜ _____.
10. **Keller, W. D., and Bundy, R. S.:** Effects of unilateral hearing loss upon educational achievement. *Child Care Health Dev*, 6(2): 93-100, 1980, *[4a]* _____ ☜ _____.
11. **Kenworthy, O. T.; Klee, T.; and Tharpe, A. M.:** Speech recognition ability of children with unilateral sensorineural hearing loss as a function of amplification, speech stimuli and listening condition. *Ear Hear*, 11(4): 264-70, 1990, *[3b]* _____ ☜ _____.
12. **Kiese-Himmel, C.:** Unilateral sensorineural hearing impairment in childhood: analysis of 31 consecutive cases. *Int J Audiol*, 41(1): 57-63, 2002, *[4b]* _____ ☜ _____.
13. **Kopun, J. G.; Stelmachowicz, P. G.; Carney, E.; and Schulte, L.:** Coupling of FM systems to individuals with unilateral hearing loss. *J Speech Hear Res*, 35(1): 201-7, 1992, *[4b]* _____ ☜.
14. **Lieu, J. E.:** Speech-language and educational consequences of unilateral hearing loss in children. *Arch Otolaryngol Head Neck Surg*, 130(5): 524-30, 2004, *[1a]* _____ ☜ _____.
15. **Local Consensus:** During BESt development timeframe. *[5]* ☜.
16. **McKay, S.:** To Aid or Not to Aid: Children with Unilateral Hearing Loss. _____ 2002, *[4b]* _____ ☜ _____.

17. **McKay, S.; Gravel, J. S.; and Tharpe, A. M.:** Amplification considerations for children with minimal or mild bilateral hearing loss and unilateral hearing loss. *Trends Amplif*, 12(1): 43-54, 2008, *[5]* _____ _____.

18. **McKay, S., and Iyer, A.:** Management guidelines for children with unilateral hearing loss. *ASHA Leader*, 10(7): 4, 2005, *[5b]* _____.

19. **Neary, W.; Kent, S.; Yeong, C. C.; and Coyne, L.:** The role of audiological testing and computed tomography in the aetiological investigation of children with permanent unilateral hearing loss. *Audiological Medicine*, 1(4): 215-223, 2003, *[4b]* _____.

20. **Niedzielski, A.; Humeniuk, E.; Blaziak, P.; and Gwizda, G.:** Intellectual efficiency of children with unilateral hearing loss. *Int J Pediatr Otorhinolaryngol*, 70(9): 1529-32, 2006, *[4b]* _____ _____.

21. **Niskar, A. S.; Kieszak, S. M.; Holmes, A.; Esteban, E.; Rubin, C.; and Brody, D. J.:** Prevalence of hearing loss among children 6 to 19 years of age: the Third National Health and Nutrition Examination Survey.[see comment]. *JAMA*, 279(14): 1071-5, 1998, *[4a]* _____ _____.

22. **Nober, L. W., and Nober, E. H.:** Auditory Discrimination of Learning Disabled Children in Quiet and Classroom Noise. *Journal of Learning Disabilities*, 8(10), 1975, *[2b]* _____.

23. **Oyler, R. F.; Oyler, A. L.; and Matkin, N. D.:** Unilateral hearing loss: demographics and educational impact. *Language Speech & Hearing Services in the Schools*, 19(2): 201-210, 1988, *[4a]* _____.

24. **Palmer, C. V., and Grimes, A. M.:** Effectiveness of signal processing strategies for the pediatric population: a systematic review of the evidence. *J Am Acad Audiol*, 16(7): 505-14, 2005, *[1b]* _____ _____.

25. **Pipp-Siegel, S.; Sedey, A. L.; and Yoshinaga-Itano, C.:** Predictors of parental stress in mothers of young children with hearing loss. *J Deaf Stud Deaf Educ*, 7(1): 1-17, 2002, *[4a]* _____ _____.

26. **Schmithorst, V. J.; Holland, S. K.; Ret, J.; Duggins, A.; Arjmand, E.; and Greinwald, J.:** Cortical reorganization in children with unilateral sensorineural hearing loss. *National Institutes of Health Public Access Author Manuscript*, 16(5): 463-467, 2005, *[3b]* _____ _____.

27. **Shapiro, I.:** Children's use of CROS hearing aids. *Arch Otolaryngol*, 103(12): 712-6, 1977, *[4b]* _____ _____.

28. **Stein, D. M.:** Psychosocial characteristics of school-age children with unilateral hearing loss. *Journal of the Academy of Rehabilitative Audiology*, 6: 12-22, 1983, *[4b]* _____.

29. **Tharpe, A. M.:** Unilateral and mild bilateral hearing loss in children: past and current perspectives. *Trends in Amplification*, 12(1): 7-15, 2008, *[5]* _____ _____.

30. **Updike, C. D.:** Comparison of FM auditory trainers, CROS aids, and personal amplification in unilaterally hearing impaired children. *J Am Acad Audiol*, 5(3): 204-9, 1994, *[4b]* _____ _____.

31. **Vartiainen, E., and Karjalainen, S.:** Prevalence and etiology of unilateral sensorineural hearing impairment in a Finnish childhood population. *Int J Pediatr Otorhinolaryngol*, 43(3): 253-9, 1998, *[4b]* _____ _____.

32. **Yoshinaga-Itano, C., and Thomson, V.:** The work of the Village: creating a new world for children with hearing loss and their families. *International Journal of Audiology*, 47 Suppl 1: S14-22, 2008, *[5]* _____ _____.

Note: Full tables of evidence grading system available in separate document:

- Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality (abbreviated table below)
- Grading a Body of Evidence to Answer a Clinical Question
- Judging the Strength of a Recommendation (abbreviated table below)

Table of Evidence Levels (see note above)

Quality level	***Definition***
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

Strength	***Definition***
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient *(direct benefit)*
4. Burden to patient of adherence to recommendation *(cost, hassle, discomfort, pain, motivation, ability to adhere, time)*
5. Cost-effectiveness to healthcare system *(balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis)*
6. Directness *(the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome])*
7. Impact on morbidity/mortality or quality of life

Supporting information

Introductory/background information

The prevalence of unilateral permanent hearing loss in school age children ranges from 0.3-5.6% *(Bess 1998 [4a], Niskar 1998 [4a])*. A population study in UK indicated a prevalence of USNHL $\geq$ 40 decibels (dB) of 9 per 10,000 population *(Neary 2003 [4b])*, while in Finland, a rate of 1.2 per 1000 population in the 1980's was reported by Vartiainen *(Vartiainen 1998 [4b])*. See Table 1.

Table 1: Prevalence Studies *(Bess 1998 [4a], Niskar 1998 [4a], Neary 2003 [4b], Vartiainen 1998 [4b], Bess 1984 [4b])*

Study	**Prevalence Rate (per 1000 population)**
(Bess 1984 [4b])	3 (> 45 dB) 13 (including milder forms of HL)
(Vartiainen 1998 [4b])	1.2
(Neary 2003 [4b])	0.9 ($\geq$ 40 dB) 1.15 (including milder forms of HL)
(Bess 1998 [4a], Niskar 1998 [4a]) (school age)	3 to 5.6

dB = decibels, HL = hearing loss

In a survey of educational audiologists *(English 1999 [4a])*, there was a slight predominance for left-sided hearing loss (53% left vs 47% right), however, the population cohort from UK had a slight predominance for right-sided hearing loss (54% right vs 46% left) *(Neary 2003 [4b])*. In the educational survey, the degrees of hearing loss were as follows: 18% mild, 17% moderate, 22% moderate to severe, 12% severe, and 29% profound. Additionally, there were co-existing conditions in a subset of children, including 13% with learning disorders, 4% with mental retardation, 3% with significant vision impairment, 2% with attention deficit hyperactivity disorder (ADHD), and 0.2% with autism.

Summary statistics from the Directors of Speech and Hearing Programs in State Health and Welfare Agencies survey from 2006 indicated 22.4% (1147/5127) of children identified with Hearing Loss through State Early Hearing Detection and Intervention programs had UHL. Among the 665 with sensorineural UHL, 22% had mild UHL, 30.5% had moderate UHL, 23% had severe UHL, 22% had profound UHL, and 2.5% had an unknown degree of UHL *(CDC 2006 [5])*.

There are a number of reasons children with USNHL may be at a disadvantage in a classroom setting. A child may have difficulty hearing or understanding speech when the speaker is on the side of the child's poor hearing ear (monaural indirect condition), particularly when the good ear is near competing speech or noise. Even in quiet environments, when hearing with two normal ears, word recognition scores are almost 20% better than if only hearing with one ear *(Lieu 2004 [1a])*. This concept is described as binaural summation. This phenomenon is also enhanced by the squelch effect, whereby two ears can suppress background noise to allow the listener to hear the primary signal or information *(Keller 1980 [4a])*.

Children with UHL have difficulty localizing sound. Since the ears are on opposite sides of the head, the distance from the sound source to each ear helps the listener figure out where the sound originated. This is due to the head-shadow effect.

Many classroom settings can be quite noisy. In fact, Nober and Nober *(Nober 1975 [2b])* reported the average intensity of 4 elementary classrooms at 65 dB. This is important if the loudness of the speaker's voice does not supercede the noise level in the classroom. The signal-to-noise ratio is a way to describe the relative differences between the speaker's volume and the background noise volume. In general, children with mild SNHL require at least 20 to 30 dB advantage of the speaker over the background noise (or a signal to noise ratio of +20 or +30 dB). Noise in the classroom can also reverberate off the walls. This further impacts the listening environment for children who are struggling auditorally to listen to instructions and teaching.

These factors have been shown to be important in studies comparing children with USNHL to hearing children. The children with USNHL had poorer performance in localizing sounds and speech recognition in noisy conditions *(Bess 1986 [4b])*. These findings also were noted to be worse as the degree of hearing loss increased. Children who had failed a grade had more difficulties understanding speech that was presented directly in front of them as compared to children with USNHL who did not fail a grade.

Children with USNHL have not been found to differ from hearing peers in cognitive measures *(Culbertson 1986 [4b])* and speech/language measures *(Stein 1983 [4b])*. However, school age children with USNHL have shown a higher rate of difficulties with school performance, with grade retention ranging from 22-36% and requiring special assistance from 12-41% *(Pipp-Siegel 2002 [4a], Bovo 1988 [4a], Oyler 1988 [4a], Bess 1984 [4b])*. Subtle differences in cognitive subtests on IQ measures have been identified in children with UHL *(Niedzielski 2006 [4b])*. Children with right sided unilateral sensorineural hearing loss may be more likely to have academic difficulties *(Oyler 1988 [4a], Hartvig Jensen 1989 [4b], Bess 1984 [4b])*. Bess et. al. 1986 found academic difficulties associated with children having UHL *(Bess 1986 [4b])*. See Table 2.

Table 2: Academic Difficulties *(Pipp-Siegel 2002 [4a], Bovo 1988 [4a], Oyler 1988 [4a], Bess 1986 [4b])*

Study	Grade retention	Additional Resource Supports
Bess and Tharpe 1986	35%	13%
Bovo 1988	22%	12%
Oyler 1988	24%	41%
Pipp-Siegel 2002	Not reported	36%

Unilateral hearing loss can be associated with structural problems with the ear, syndromes, and congenital cytomegalovirus (CMV). Therefore, children with unilateral hearing loss warrant etiologic work-ups and medical care similar to that among children with bilateral hearing loss *(Lieu 2004 [1a])*.

Prior to universal newborn hearing screening (UNHS), children with unilateral hearing loss were identified at school age. The literature primarily focuses on this group of children. With the implementation of UNHS, the age of identification of unilateral hearing loss may decrease for many children. However there is no evidence regarding the management of unilateral hearing loss in the very young child. Based on data from Colorado's early intervention *(Yoshinaga-Itano 2008 [5])* and the findings of functional MRI (fMRI) data on cortical reorganization on side of hearing loss *(Schmithorst 2005 [3b])* this will be an important area for clinical research.

Appendix 1: Tips for Children with Unilateral Hearing Loss

What is unilateral hearing loss (UHL)?

Your child has been diagnosed with a unilateral hearing loss. UHL means there is a normal hearing loss in one ear and a hearing loss in the other. It can range from mild to total hearing loss. Hearing loss affects everyone differently. Here is some information to help you understand more about UHL and tips on how you can help your child listen better.

What are some common side effects of UHL?

- Having trouble figuring out where a sound is coming from
- Difficulty hearing the soft sounds of speech and language
- Some children may be a little slow to meet some speech and language milestones on time
- Not understanding what people are saying when you are in noisy places
- Unable to pay attention for a long period of time, trouble keeping focused, because they have to work harder to listen
- Having a hard time following directions that include more than one piece of information
- May become tired more easily (from listening with only one normal hearing ear)
- May develop subtle speech, language, or learning difficulties

How can I help develop my child's speech and language?

Here are some things you can do to help your child develop his speech and language skills

- Go down to child's level, get the child's attention, make eye contact, and follow child's eyes
- Position yourself near the good ear and speak clearly
- Keep background noise down to a minimum (turn down the TV, radio, etc)
- Talk about what is happening now, the activities that the child is engaged in, and daily routines
- Talk about what you are doing (e.g. "I am washing the table, so we can eat lunch."
- Imitate and expand your child's statements by a word or a phrase to help build language skills (e.g. child, "milk" then parent, "More milk? Here is more milk.")
- When giving the child a direction, speak a little slower and pause between the parts of the direction (e.g. "Please find your shoes…then get your coat.").
- Ask the child to repeat what you have said to check that all of the direction was understood (e.g. "What do you need to do after you find your shoes?").
- To encourage vocabulary growth, talk about and describe objects and actions in different ways and provide a lot of experiences with books (e.g. child, "pretty flower." Parent, "Yes that is a pretty flower. That flower is a daisy.")
- Observe your child's reactions to know if information is understood, especially in noisy environments. Ask questions to make sure your child understood
- Help your child turn the good ear to the speaker or stand close to others so that peers can be heard during play.
- Have your child's speech and language development checked on a regular basis as recommended or if there are concerns.

How can I develop my child's listening skills?

Here are some things you can do to help your child develop his listening skills:

- Position yourself in front of your child's face – to teach use of visual cues at an early age.
- Have your child look at the person who is speaking to him.
- Place your infant/child's car seat in a position that makes the speaker's voice closest to the better hearing ear – if you are the passenger, sit in the back seat next to your child , while still following car seat regulations
- Have your child look at the person who is speaking to him.
- Limit the amount of background noise and visual distractions (e.g., turn off the TV, radio)
- Read books and talk on the side of the better hearing ear.
- Teach your child to find the best spots to listen and learn!
- Educate caregivers/teachers about the degree of hearing loss and what they can do to better help your child listen and learn.

Here are some things you can do to help make a better listening environment for your child:

- Become aware of the noises that are in your child's environment and limit the amount of background noise. Some common noise sources are: TVs, radios, open windows, fans, dishwashers, microwave, running water and a hair dryer.
- Evaluate the listening environment and make any changes that would most benefit your infant/child. Some examples are:
    - **restaurant** – ask for a seat away from the kitchen door – place the infant/child w/ better hearing ear towards the primary speaker -if possible, have your child's back to the wall and ensure good lighting
    - **auditorium or large room** – have your child sit near the middle, at the front of the room (good visual position) and away from other sound sources
    - **classroom** – ask that tennis balls placed on feet of desks/chairs, add area rugs or curtains to absorb sound. Identify competing sound sources (air conditioner, fans, pencil sharpeners, computer terminals, etc) and make sure child is not seated near them.
- Openly talk about where you are placing your child so the child learns how to make these decisions for himself. (e.g. "Let's think about the best place to sit in the restaurant" or "That radio is too loud. Let's turn it off so we can talk.")
- Use earplugs to protect against loud sounds (fireworks, lawnmowers, music, etc).

Check with the Ears, Nose, Throat doctor (ENT, or otolaryngolgist) and/or audiologist

- When you feel additional support is needed, like amplification (hearing aids) or FM devices.
- To have your infant/child's hearing tested more frequently to watch for possible changes.
- Whenever your child has an ear infection.

Appendix 2: Summary of Evidence

Study Citation	Study Type/ Design	N	Setting	Patients	Intervention	Comparison	Outcomes
(Kenworthy 1990 [3b])	Prospective cohort Repeated measures design with self as control	6	Simulated sound in regular classroom	8 to 12 year olds with 56 to 120 dB UHL	No amplification vs FM system vs CROS aid	Self as own control Speech recognition in monaural indirect, monaural direct, mid-line signal/omni-directional noise	5 of 6 children • severe to profound UHL • showed significant gains in speech recognition scores with FM system • likely to be academically unsuccessful 6th child • milder UHL • better able to cope under adverse listening conditions generalization of conclusion is limited
(Updike 1994 [4b])	Prospective cohort self as own control	6	Regular classroom	Children with mild to profound UHL 5 to 12 year olds Equal distribution of side of HL	FM vs CROS aid vs HA	Self as own control Listening in quiet environments & those with background noise +6dB S/N ratio	• All experienced significant difficulty with word recognition in typical classroom environment. • With FM showed improved word recognition in background noise environment compared to • CROS aid and HA which offered no improvement, actually showed detrimental effect.
(Flexer 1994 [3b])	Prospective Cohort	282	12 regular classrooms (6 regular Kinder-garten and 6 regular first grade)	None of the students were diagnosed with hearing impairment	FM sound field amplification systems – high fidelity public address self-contained wireless systems contained in single classroom 13 question parent questionnaire	3 classrooms of each grade were amplified 3 kindergarten classrooms amplified compared to 3 non-amplified and 3 first grade classrooms amplified compared to 3 non-amplified classrooms	• Based on questionnaire – 75% of 93 of the 282 children reported having had 6 or more ear infections, leaving them with fluid in their middle ear placing them at significant risk for academic failure • 25% of the entire 282 had extensive & continuous history of ear & hearing problems • 25% to 33% of the typical kindergartener or first grader were not hearing clearly word sound distinctions o 33% failed the fall screening o 36% failed the 1st winter screening o 34% failed the 2nd winter screening o 27% failed the spring screening
(Kopun 1992 [4b])	Prospective cohort study	15	Experiment conditions	5 to 13 year olds with UHL (degree of HL not defined)	Effects of various occlusions by FM system	Calculation of attenuation characteristics of delivery systems	• Occlude $\leq$ 30% of the ear canal. • Best fit for FM system - most open fit. • Tube fitting - only option that is non-occlusive. • Lightweight headphones produce $\leq$ 5dB of attenuation through 4000Hz.
(Shapiro 1977 [4b])	Longitudinal case series	10	Clinical setting	7 to 17 year olds, Most profound UHL	CROS Aid	Questionnaire after 1 month of use No comparison group	• 7 of 10 were “successful users” • Defined as reported regular use • Improvement in academic performance as rated by the teachers

Study Citation	Study Type/ Design	N	Setting	Patients	Intervention	Comparison	Outcomes
(Kiese-Himmel 2002 [4b])	Descriptive Case series Retrospective chart review to identify parents for survey	31	Hospital based	Parents of 1 to 10 year olds with > 30dB UHL (majority severe to profound)	Survey determining acceptance of amplification (HA)	No comparison group	• 80% of children accepted HA, • Those with severe to profound UHL were less likely to accept the HA
(McKay 2002 [4b])	Case series	28	Hospital based	Parents of children 2 to 17 year olds with mild-moderately severe UHL	Survey determining benefit of HA	No comparison group	72% reported benefits, specifically improvements in: • hearing, • social settings and • academic settings
(McKay 2005 [5b])	Non Peer-reviewed Management Guideline	N/A	ASHA guidelines	Clinical experience at Children's Hospital of Philadelphia a audiology, based on literature review	HA, FM	N/A	Candidates for amplification: • Mild to moderately severe (25 to 65 dB HL) sensory or permanent conductive HL in one ear • 3 ≥ or < 3 if frequency-specific threshold information is available FM systems for all with • UHL including those with severe to profound HL or • poor word recognition abilities Bone conduction and CROS systems not standard recommendation, but based on a case-by-case if appropriate
(Tharpe 2008 [5])	Systematic review	N/A	Clinical populations	Children with UHL	HA, FM	N/A	• Make sure HA does not interfere with speech perception related to unaided condition • Amplify at HL of 65dB or less • Consider FM candidacy when: o demonstrates poorer than expected performance on speech-in-noise tasks o poorer than expected academic performance in the classroom, o increased listening fatigue and/or o decreased listening ability in difficult acoustic environments. • Consider in decision: o environment in which device will be used, o age of child, o degree and configuration of HL & use of HA.

Study Citation	Study Type/ Design	N	Setting	Patients	Intervention	Comparison	Outcomes
(Lieu 2004 [1a])	Systematic Review	N/A	N/A	Children with UHL	HA, FM	N/A	Risk factors for educational problems: • early age of UHL onset, • perinatal and/or • post-natal complications, • severe to profound SNHL, • right UHL Interventions in children with UHL: • Preferential classroom placement, • parental education, • child education, • teacher education, • screening for speech and language delays/ difficulties/ amplification Consider amplification, FM systems, HA, CROS aids, or bone conduction aids if any signs of: • speech-language delay, • struggling in school or • struggling in social interactions. Tailor device to the needs of the individual child. Screen school-age children for educational problems at routine intervals Follow-up audiograms at least annually to monitor for progression of hearing loss; repeat audiograms if any change in hearing is suspected

ASHA – American Speech -Language - Hearing Association, CROS – contralateral routing of signal, dB – decibel, FM – frequency modulation, HA – hearing aid, HL – hearing loss, Hz – hertz, N/A – not applicable, UHL – unilateral hearing loss

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Clinical Effectiveness Support:
Eloise Clark, MPH, MBA, Guidelines Program Administrator
Karen Vonderhaar, MS, RN, Methodologist

Search strategy

Database: Ovid MEDLINE (R), 1996 to January Week 2 2008

1 child/or school aged children.mp (376492)
2 ex hearing loss/ or exp hearing loss, unilateral/ (15898)
3 amplifiers/ (294)
4 (outcomes or educational performance or school performance or functional outcomes$).mp. [mp=title, original title, abstract, name of substance word, subject hearing word} (251435)
5 (#1 and #2 and #3 and #4).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (251435)
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9 Hearing loss/or hearing loss unilateral/ (2519)
10 (Hearing Loss or unilateral or hearing disorder$).mp. [mp=title, original title, abstract, name of substance word, subject heading word} (47371)
11 1 and 3 and 4 and 7 and 10 (0)
12 4 and 7 and 10 (12
13 1 and 12 (6)
14 From 13 keep 1-6 (6)

Limits: Humans, English, Child: 6-12 years
Amplification OR digital hearing aid OR fm system OR baha OR cros link aid (2648)
Unilateral hearing loss (63)
(Educational OR school) AND (outcomes OR performance) (5144)
(Educational OR School) AND (outcomes OR performance) AND unilateral hearing loss AND (amplification OR digital aid OR FM system OR baha OR Cros link aid) (1)
(unilateral hearing loss) AND systematic[sb] (6)

Known conflicts of interest

Conflicts of interest were declared and none were found.

Applicability issues

Outcome measures to be monitored include:

1. Access to sound (categories of fair, good or excellent based on real ear and sound field audibility measures)
2. Auditory Perception and Skills (rated by the Auditory Skills Checklist © or other functional measure)
3. Improvement in Everyday Listening Skills (rated by the Meaningful Auditory Integration Scale)
4. Patient Independence (Questionnaire filled out by child or parent)
5. Care Plan Adherence (report adhering to care plan to at follow-up visit)
6. Parental Stress Index-Short Form
7. Quality of Life (Peds QL)

Copyright Statement

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Reviewed by: Clinical Effectiveness

Cochlear implantation in single-sided deafness for enhancement of sound localization and speech perception

Sally M. Kamal, Aaron D. Robinson, and Rodney C. Diaz

Purpose of review
To examine the current literature regarding application of cochlear implantation in patients with single-sided deafness for improvement in sound localization.

Recent findings
As familiarity of the technical and biological capabilities of cochlear implantation improves and criteria for use broaden, investigators have begun examining usage of cochlear implantation in patients with single-sided deafness as a viable solution in attempts to improve sound localization and speech perception. Although studies of such application are limited, from the available published literature, modest benefits have been described in both sound localization and speech perception. Patients consistently report improvement in quality of life after cochlear implantation for single-sided deafness.

Summary
Although single-sided deafness is not a currently approved indication for cochlear implantation, limited investigational studies to date have demonstrated patient improvement in both sound localization and speech perception.

Keywords
bone anchored hearing system, cochlear implant, contralateral routing of signal, interaural level difference, interaural phase difference, interaural time difference, single-sided deafness, squelch effect, summation effect, unilateral hearing loss

INTRODUCTION

Historically, patients with single-sided deafness did not have surgical treatment options, and rehabilitation of hearing on the deaf side was accomplished only with specialized hearing aids allowing contralateral routing of sound or signal (CROS). With the advent of bone-anchored hearing systems (BAHS), the low attenuation of sound signal across the skull base allows exploitation of contralateral routing of signal through the skull base bone rather than electronically across hearing aid devices.

Current therapies for rehabilitation of hearing in patients with single-sided deafness are thus limited to these two modalities: CROS and BAHS. Both CROS and BAHS solutions are effective in addressing the head shadow effect and restoring sound awareness to the deafened side in such patients. However, both available solutions provide minimal to no benefit with regards to sound localization and provide only limited improvement in speech perception, especially when ambient noise is abundant [1]. Regardless of the modality of signal routing, both techniques rely on usage of the remaining hearing ear contralaterally to allow awareness of sound on the deaf side, rather than repairing or replacing the intrinsic auditory sensor, the cochlea, on the deafened side. As a result, patients with single-sided deafness have similar auditory deficiencies as patients who have congenital unilateral deafness. Namely, these patients have specific difficulty with sound localization and speech perception, especially when exposed to noise [2].

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Curr Opin Otolaryngol Head Neck Surg 2012, 20:393–397
DOI:10.1097/MOO.0b013e328357a613

KEY POINTS

- Two independent acoustic sensors are required for optimization of psychoacoustic strategies for sound localization and speech perception.
- Current approved treatment solutions for hearing rehabilitation of unilateral hearing loss [contralateral routing of sound or signal (CROS), bone-anchored hearing system (BAHS)] allow sound awareness on the deafened side but do not replace the intrinsic mechanism of hearing on that side, and thus do not provide true rehabilitation of azimuthal sound localization and binaural speech perception strategies.
- Cochlear implantation provides true replacement of an independent acoustic sensor to the deafened side in unilateral hearing loss.
- Limited studies of cochlear implantation in unilateral hearing loss have demonstrated evidence of improvement over unaided, CROS, and BAHS solutions in azimuthal sound localization and binaural speech perception strategies.

As cochlear implantation has improved and familiarity with the device has increased, selection criteria for implantation have broadened. Bilateral cochlear implantation in patients with bilateral profound sensorineural hearing loss is performed increasingly and allows such patients the benefits of binaural hearing. However, patients with unilateral severe to profound deafness are currently not surgical candidates for cochlear implantation, and as a result they are not afforded the same benefits of binaural hearing. This article reviews current literature regarding investigations of cochlear implantation in those with unilateral profound sensorineural hearing loss and discusses the implications of such technology on potential improvement of the auditory deficiencies seen in these patients.

SOUND LOCALIZATION

Binaural hearing allows accurate sound localization, specifically azimuthal sound localization, by simultaneous utilization of multiple psychoacoustic phenomena: interaural phase differences (IPDs), interaural time differences (ITDs), and interaural level differences (ILDs). These psychoacoustic phenomena rely on the use of two independent acoustic sensors. In those with single-sided deafness, the advantages of IPD, ITD, and ILD effects cannot be realized. Vertical or altitudinal localization of sound sources will not be discussed here, as the auditory system utilizes both binaural and monaural strategies, as well as dynamic strategies, for this form of sound localization.

The auditory system exploits the differences of sound arrival between the ears to help calculate location: sound sources biased towards one side of the head will arrive at different times and phases between the left and right ears. Sounds that are sourced off-axis will arrive at different phases to each of the ears, and sound signals at frequencies low enough to allow unambiguous discrimination of phase difference, that is whose wavelengths are at least twice the length as the interaural distance, are cross-correlated by the auditory system to calculate an azimuthal location of the sound source. The cross-correlation method of IPD calculation of sound source localization is effective for signals below approximately 800 Hz, given the typical size of the human head and approximate distance between human ears.

The actual onset of arrival of a sound feature, that is the blast from an explosion, or a phoneme in speech, will differ between ears for off-axis sound sources; the auditory system utilizes this group delay form of ITD, which is optimized for higher-frequency signals above 16 kHz, as another modality for calculating azimuthal sound location. Between 800 and 16 kHz, the human auditory system utilizes a combination of IPD or phase delay and ITD or group delay phenomena.

Interaural level differences are sensed by the binaural auditory system when sound is presented off-axis and biased towards one side of the head. The auditory system is able to interpret the difference in sound amplitude between the ears and calculate an azimuthal location to the sound source.

Clearly then, azimuthal localization of sound sources is inherently dependent on psychoacoustic phenomena employing two independent acoustic sensors. In most humans, these would be the normally functioning cochleae. In patients with unilateral hearing loss, azimuthal sound localization is not possible unless an independent acoustic sensor can be positioned to take the place of the deafened cochlea.

In a study comparing sound localization of 11 patients with acquired unilateral deafness, Arndt *et al.* [3▪▪] evaluated sound localization between three strategies: with a CROS hearing aid, with a BAHS implant, and with a cochlear implant 6 months after implantation. To assess accuracy and effectiveness, seven loudspeakers were placed at 30 degree intervals from −90 degrees to +90 degrees in a semicircle in front of the patients. Sound stimuli were then presented and patients asked to identify the speaker from which the sound was delivered, utilizing each of the three strategies.

The Laryngoscope

The Triological Society
Best Practice

Optimal Management of Single-Sided Deafness

Hwa J. Son, MD; Daniel Choo, MD

BACKGROUND

Current trends in auditory rehabilitation for single-sided deafness (SSD) reflect a renewed interest in the functional impact of unilateral hearing loss and also in the advances in technologies for SSD that make interventions more effective and more appealing to patients. Clinicians are now equipped with an array of therapeutic options ranging from Bluetooth contralateral routing of signal (CROS) devices to in-the-ear TransEar hearing aids (Ear Technology Corp., Johnson City, TN), as well as bone-anchored hearing aids (BAHA). Even unilateral cochlear implantation represents a current investigational intervention that may offer yet another option to patients in the future.

A prominent deficiency in this field is the absence of concise and evidence-based guidelines for patient and intervention selection. Factors to consider when recommending the best treatment include functional handicapping due to SSD, speech understanding in noise, localization, ease of use, the need for surgery and cost. This article seeks to review the pertinent literature on this topic and offer a best-practice framework.

LITERATURE REVIEW

Both BAHA and CROS devices enable patients to pick up sound from the deaf side, thus effectively expanding the sound field.[1] Patients are bothered by the occlusion effect a CROS device presents by having an ear mold in their better hearing ear, whereas some reject the BAHA because of the need for surgery. Niparko et al.[1] compared both objective and subjective measures on 10 patients with SSD who underwent a 1-month trial period with a conventional CROS device and subsequent BAHA implantation. All quality-of-life measure tests showed greater subjective satisfaction with the BAHA compared to the CROS device. The localization test showed poor performance across the board, with no statistical difference among unaided, CROS device, and BAHA, but the BAHA was superior for speech discrimination in noise. It was conjectured that the speech in noise performance was better with the BAHA compared to the CROS device due to the tighter and more efficient transcranial routing of sound from osseointegration.

The TransEar hearing aid offers a nonsurgical bone-conduction hearing aid option that can be inserted in the algorithm in addition to the BAHA and CROS device for some patients. The TransEar requires a deeply fitted ear mold that allows bone transmission of sound by means of an in-the-ear hearing aid but eliminates occlusion in the better hearing ear as in the CROS device. To date, there remains a paucity of data about its use in the literature, and audiologic familiarity/expertise is required to make this an effective hearing rehabilitative option.

A prospective pilot study conducted in Europe by Hol et al.[2] had 10 subjects with SSD use all three devices: the BAHA soft band, CROS device, and a device that is placed completely in the canal (CIC), in a random order for an 8-week trial period each. The localization was poor across the board, but the results on quality-of-life issues were mixed with some surprising benefits with the CIC device. At the end of trying all three devices, only 3/10 of the patients chose to proceed with BAHA implantation and 1/10 for a CROS device. The authors emphasized that all patients derived some form of benefit for each device, but there is a real need for a sufficient trial period for patients before making an informed decision.

Complications and long-term satisfaction with the BAHA needs to be considered before committing to a surgery. Gluth et al.[3] summarized a long-term satisfaction and complication rate of the BAHA, with average use duration of 3.5 years. Seventy percent of all users thought their overall quality of life improved, which was maintained at long term with an 81% continued-user rate for the BAHA. For complications, 38% of patients experienced skin reactions, whereas 66.7% required the processor to be repaired. This article highlights the fact

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Editor's Note: This Manuscript was accepted for publication May 11, 2012.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.23483

Bone Anchored Hearing Aids

Questions:

1) Should bone anchored hearing aids (BAHA) continued to be covered? Should coverage be for unilateral or bilateral hearing loss or both? Should any restrictions be placed on BAHA use via a guideline?

Question source: OHP Medical Directors

Background**:**

There are three types of hearing loss: conductive, sensorineural, and mixed. Conductive hearing loss involves the outer and middle ear and sound is mechanically or physically blocked; it is often corrected through medical or surgical intervention. Sensorineural hearing loss is also referred to as nerve hearing loss, involves damage to the cochlea (i.e., inner ear) or the eighth cranial nerve, and can have various etiologies including aging, viral or bacterial infections, trauma, or exposure to loud noises. Sensorineural hearing loss is not normally corrected through medical or surgical methods and is often treated with a hearing aid. Mixed hearing loss refers to conductive hearing loss and sensorineural hearing loss.

Hearing aids are used to amplify and deliver sounds. There are different categories of hearing aids including conventional hearing aids, bone conduction devices, middle-ear implants, and bone-anchored hearing aids (BAHA). Conventional hearing aids can be behind the ear, in the ear, in the ear canal, completely-in–the-canal (CIC), on the body, or contralateral routing of signal. Several factors are considered when determining which type of hearing aid is most appropriate for individuals, including degree of hearing loss, work setting, and acceptance of hearing loss.

CIC hearing aids are hearing aids that fit almost entirely in the canal. They are small in size and are deeply placed, thus, the number of output and response controls are limited and there is no directional microphone. The BAHA are surgically implanted to the inner ear and operate on bone-conducted auditory stimulation. A titanium fixture is surgically implanted into the temporal bone of the skull. The hearing devices transmit sound directly to the inner ear through the temporal bone, bypassing the external auditory canal and middle ear.

Issue: currently, BAHA (CPT 69714, 69715) is located on the “hearing aid” lines (Line 317 HEARING LOSS - AGE 5 OR UNDER; Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS, Line 450 HEARING LOSS - OVER AGE OF FIVE Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS)

69714 Implantation, osseointegrated implant, temporal bone, with percutaneous attachment to external speech processor/cochlear stimulator; without mastoidectomy

69715 with masoidectomy

From Tracy Muday, OHP Medical Director

This issue has surfaced again. One of the kids that we approved for 69714--implantation, osseointegrated implant, temporal bone, with percutaneous attachment to external speech processor/cochlear stimulator, without mastoidectomy—has not yet had surgery. She has normal hearing in one ear and atresia of the other ear canal. She is 10.

We now have a request to change the code to 69710--implantation or replacement of electromagnetic bone conduction hearing device in temporal bone. As I mentioned before, this CPT code pairs only with line 590—conductive hearing loss, and line 448—complications of a procedure usually requiring treatment.

Should the 69710 be added to the covered hearing loss lines, or should I consider that the hearing loss or the ear canal atresia are covered comorbid conditions? I'll go ahead and approve the procedure, I'm asking primarily for housekeeping purposes whether the CPT code should reside on the covered line. It might be helpful for others in the future.

Evidence**:**

1) **Canadian Agency for Drugs and Technology in Health HTA 2010**
    - **a.** One health technology assessment, one systematic review, and three observational studies were identified for BAHA.
    - **b.** Limited evidence was identified regarding the acoustic and non-acoustic benefits of BAHA. The relevant included evidence was mainly observational studies which are associated with higher risk of bias. The health technology assessment from 2006 indicated that using BAHA for unilateral sensorineural hearing loss, bilateral implantation, and tinnitus were considered experimental patient indications. The authors of the systematic review indicated that due to the lack of evidence, caution should be used when advising patients on the non-acoustic benefits of the BAHA.
2) **Colquitt 2011**, British HTA/systematic review and economic assessment of BAHA
    - **a.** 12 studies (reported in 15 publications) were included in the review of clinical effectiveness (seven cohort pre–post studies and five cross-sectional audiological comparison studies). No studies with a control group were identified. Seven studies compared BAHAs with conventional hearing aids, three of these and one additional study compared BAHAs with unaided hearing, and four studies compared unilateral and bilateral BAHAs. No prospective studies comparing BAHAs with ear surgery were identified. The overall quality was rated as weak for all included studies and meta-analysis was not possible due to differences in outcome measures and patient populations.
    - **b.** Economic analysis: The incremental cost per user receiving a BAHA, compared with BCHA, was £16,409 for children and £13,449 for adults.

The cost per case successfully treated with a BAHA was estimated at £ 18,681 for children and £ 15,785 for adults, over a 10-year time horizon. In an augmented, exploratory analysis the incremental cost per QALY gained was between £ 55,642 and £ 119,367 for children and between £ 46,628 and £ 100,029 for adults for BAHAs compared with BCHA

c. Conclusions: The available evidence is methodologically weak and the results have a high risk of bias. As such, there is a high degree of uncertainty about the conclusions of this systematic review. The findings suggest that hearing is improved with BAHAs compared with no hearing aid, and although there are audiological benefits of BAHAs when compared with conventional (bone conduction hearing aid) BCHAs, the audiological benefits of BAHAs when compared with conventional hearing aids/air conduction hearing aid (ACHAs) are less clear. Limited data suggest an improvement in QoL with BAHAs when compared with conventional aids, but there is an absence of evidence regarding other potential benefits, such as length of time the aid is able to be worn and improvement of discharging ears. The evidence suggests that there are some benefits of bilateral BAHAs compared with unilateral BAHAs. The results of our cost analysis demonstrate that BAHAs are significantly more costly than conventional BCHAs. The additional costs continue while individuals remain using their BAHA and are not restricted to the initial processes of surgical implantation and fitting of the BAHA sound processor. Our exploratory cost-effectiveness analysis of BAHAs versus BCHAs suggests that BAHAs are unlikely to be a cost-effective option where the benefits (in terms of hearing gain and probability of using of alternative aids) are similar for BAHAs and their comparators

3) **Stalfors 2011**, Swedish HTA of BAHA for unilateral hearing loss
   - **a.** Evaluation of BAHA vs contralateral routing of signals (CROS) or no hearing device in patients with profound unilateral hearing loss
   - **b.** one randomized controlled trial (RCT) and two cohort studies evaluating speech recognition and sound localisation ability with BAHA and (contralateral routing of signals) CROS (N=77 total). The studies did not show any outcome differences between BAHA, CROS or no treatment in terms of speech recognition or sound localisation. The level of evidence according to the GRADE system for BAHA being superior to CROS or no hearing device for unilateral profound hearing loss regarding the outcomes speech recognition and sound localisation is very low.
   - **c.** Four studies evaluated the subjective benefit of BAHA and CROS, one RCT and three cohort-studies. The studies did not show any outcome differences between BAHA, CROS or no treatment. The level of evidence according to the GRADE system for BAHA being superior to CROS or no hearing device for unilateral profound hearing loss regarding the outcome subjective benefit is very low (GRADE).
   - **d.** No serious complications following surgical implantation of BAHA have been reported. The most common adverse effects and complications of

BAHA surgery are postoperative skin reaction which varies between 3 –30 %, and implant loss which varies between 1- 14%.

Other policies

1) **Aetna 2014**
    a. Aetna considers implantable bone-anchored hearing aids (BAHAs) or temporal bone stimulators medically necessary prosthetics for persons aged 5 years and older with a unilateral or bilateral conductive or mixed conductive and sensorineural hearing loss who have any of the following conditions, where the condition prevents restoration of hearing using a conventional air-conductive hearing aid and who meet the audiologic criteria below:
        i. Congenital or surgically induced malformations of the external ear canal or middle ear (such as aural atresia); *or*
        ii. Dermatitis of the external ear, including hypersensitivity reactions to ear moulds used in air conduction hearing aids; *or*
        iii. Hearing loss secondary to otosclerosis in persons who can not undergo stapedectomy; *or*
        iv. Severe chronic external otitis or otitis media; *or*
        v. Tumors of the external ear canal and/or tympanic cavity; *or*
        vi. Other conditions in which an air-conduction hearing aid is contraindicated.
    b. Audiologic criteria:
        i. Unilateral implant: Conductive or mixed (conductive and sensorineural) hearing loss with pure tone average bone conduction threshold (measured at 0.5, 1, 2, and 3 kHz) less than or equal to 45 dB HL (BAHA Divino, BAHA BP100), 55 dB HL (BAHA Intenso, Cochlear Baha 3 Power [BP110]) or 65 dB HL (BAHA Cordelle II).
        ii. Bilateral implant: Moderate-to-severe bilateral symmetric conductive or mixed (conductive and sensorineural) hearing loss, meeting above-listed bone conduction thresholds in both ears. Symmetric bone conduction threshold is defined as less than:
            1. 10 dB average (measured at 0.5, 1, 2 and 4 kHz) or less than 15 dB at individual frequencies (BAHA Divino, BAHA BP100); *or*
            2. 10 dB average difference between ears (measured at 0.5, 1, 2, and 3 kHz), or less than a 15 dB difference at individual frequencies (BAHA Cordelle II, BAHA Intenso).
    c. Aetna considers the use of an implantable BAHA medically necessary in persons with unilateral sensorineural hearing loss (single-sided deafness, i.e., deafness in one ear while the other ear has normal hearing).
    d. Aetna considers the use of an implantable BAHA experimental and investigational for bilateral pure sensorineural hearing loss, and for all

other indications becuase its effectiveness for indications other than the ones listed above has not been established.

2) BCBS 2014

a. An implantable bone-anchored hearing aid is considered **medically necessary** as an alternative to an air conduction hearing aid for individuals five years of age and older who meet **both** audiologic and medical condition criteria as follows:

i. Audiologic criteria (must meet **one**):

1. Bilateral implant: Moderate to severe bilateral symmetric bone conductive or mixed (conductive and sensorineural) hearing loss. Symmetric bone conduction threshold is defined as less than:
    a. 10 decibels (dB) average difference between ears (measured at 0.5, 1, 2, and 4 kilohertz [kHz]), or less than a 15 dB difference at individual frequencies (BAHA Divino™); **or**
    b. 10 dB average difference between ears (measured at 0.5, 1, 2, and 3 kHz), or less than a 15 dB difference at individual frequencies (BAHA Cordelle II; BAHA BP100; BAHA Intenso™); **OR**
2. Unilateral implant: Conductive or mixed (conductive and sensorineural) hearing loss with pure tone average (PTA) bone conduction hearing threshold better than or equal to 45 dB hearing loss (HL) (BAHA Divino, BAHA BP100), 55 dB HL (BAHA Intenso), or 65 dB HL (BAHA Cordelle II).

ii. Medical condition criteria (must meet **at least one**):

1. Congenital or surgically induced ear malformations of the external or middle ear canal (e.g., atresia); **or**
2. Severe chronic external otitis or otitis media; **or**
3. Tumors of the external ear canal or tympanic cavity; **or**
4. Dermatitis of the external ear canal, including reactions from ear molds used in air conduction hearing aids; **or**
5. Other anatomic or medical conditions that contraindicate the use of an air conduction hearing aid.

b. An implantable bone-anchored hearing aid is considered **medically necessary** to improve speech recognition in individuals five years of age and older with unilateral sensorineural hearing loss (i.e. single sided deafness) while the other ear has normal hearing. Normal hearing is defined as PTA air conduction (AC) threshold equal to or better than 20 dB HL at 0.5, 1, 2, and 3 kHz.

c. A transcutaneously worn BAHA (bone conduction-type hearing aid) utilizing a Headband or Softband is considered **medically necessary** as an alternative to an implantable bone anchored hearing aid or air conduction hearing aid in individuals who meet the criteria specified in either (A) **or** (B), above, except for the age limitation of 5 years of age and older which does not apply for a transcutaneously worn BAHA.

Summary: The evidence for BAHA improving sound localization, speech recognition, or other outcomes compared to other types of hearing aids or no treatment is extremely limited. Evidence is limited if BAHA should be unilateral or bilateral. Most major recommendation statements have BAHA as a second line therapy. There is controversy in the literature and major recommendation statements about whether BAHA should be used to treat sensorineural hearing loss.

HERC staff recommendations:

1) Make no change in the placement of the CPT codes for BAHA placement (69714, 69715)
    a. Alternative: remove BAHA from current lines due to evidence of other therapies being equally effective but lower cost/risk.
    b. Note: to remove a therapy from the Prioritized List requires evidence of lack of effectiveness, a higher bar than for adding a therapy to the List
2) Adopt the following new guideline for lines 317 and 450

GUIDELINE NOTE XXX BONE ANCHORED HEARING AIDS

Lines 317, 450

Bone anchored hearing aids (BAHA, CPT 69714, 69715) are included when the following criteria are met:

1) The patient is age 5 years or older
2) Treatment is for unilateral severe to profound hearing loss when the contralateral ear has normal hearing
3) Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective.
4) Implantation is unilateral.

Use of BAHA for treatment of tinnitus is not covered.

TITLE: Completely-in-the-Canal and Bone Anchored Hearing Aids: A Review of the Clinical Effectiveness and Cost-Effectiveness

DATE: 4 March 2010

CONTEXT AND POLICY ISSUES:

Hearing loss affects people of all ages.[1] It can be classified as mild, moderate, severe, or profound based on decibels (dB) hearing loss (dBHL).[1] Mild hearing loss is between 26 dBHL and 40 dBHL, moderate is between 41 dBHL and 70 dBHL, severe is between 71 dBHL and 90 dBHL, and profound hearing loss is 91 dBHL or greater.[1]

There are three types of hearing loss: conductive, sensorineural, and mixed.[1] Conductive hearing loss involves the outer and middle ear and sound is mechanically or physically blocked; it is often corrected through medical or surgical intervention.[1] Sensorineural hearing loss is also referred to as nerve hearing loss, involves damage to the cochlea (i.e., inner ear) or the eighth cranial nerve, and can have various etiologies including aging, viral or bacterial infections, trauma, or exposure to loud noises.[1] Sensorineural hearing loss is not normally corrected through medical or surgical methods and is often treated with a hearing aid.[1] Mixed hearing loss refers to conductive hearing loss and sensorineural hearing loss.

Hearing aids are used to amplify and deliver sounds.[1] There are different categories of hearing aids including conventional hearing aids, bone conduction devices, middle-ear implants, and bone-anchored hearing aids (BAHA).[1] Conventional hearing aids can be behind the ear, in the ear, in the ear canal, completely-in–the-canal (CIC), on the body, or contralateral routing of signal. Several factors are considered when determining which type of hearing aid is most appropriate for individuals, including degree of hearing loss, work setting, and acceptance of hearing loss.

CIC hearing aids are hearing aids that fit almost entirely in the canal. They are small in size and are deeply placed, thus, the number of output and response controls are limited and there is no directional microphone.[1] The BAHA are surgically implanted to the inner ear and operate on bone-conducted auditory stimulation. [1-3] A titanium fixture is surgically implanted into the temporal bone of the skull. [2,3] The hearing devices transmit sound directly to the inner ear

through the temporal bone, bypassing the external auditory canal and middle ear.[2] Both the BAHA and CIC hearing aid have been approved for use by Health Canada.[4]

In some occupations adults are exposed to a higher risk of noise-induced hearing loss.[5] In addition, Canadians may be employed in environments that require special electronic equipment, special uniforms and helmets, and work in areas considered outside of normal day-to-day activities for the regular citizen. This report will review evidence regarding the clinical effectiveness and cost-effectiveness of CIC hearing aids and BAHA for adults less than 60 years of age across a variety of situations.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of completely-in-the-canal and bone anchored hearing aids?

2. What is the cost-effectiveness of completely-in-the-canal and bone anchored hearing aids?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID Medline, PubMed (supplemental search), The Cochrane Library (Issue 1, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2005 and February 2010. No filters were applied to limit the retrieval by study type.

To be considered for inclusion, observational studies were required to be prospective, include a minimum of 10 patients, and have at least 50% of the study sample suffering from sensorineural hearing loss. Outcomes of interest for this report included acoustic benefits, non-acoustic benefits (e.g., quality of life), durability, use in different environments (e.g., international countries), and infection rates.

SUMMARY OF FINDINGS:

One health technology assessment,[3] one systematic review,[6] and three observational[7-9] studies were identified for BAHA. No RCTs, controlled clinical trials, or economic studies were identified. No relevant studies were identified for CIC hearing aids. No relevant studies were identified for specific occupations that may have unique needs. Definitions for the non-acoustic measures used in the included studies can be found in Appendix 1. Additional information on the included studies is reported in the tables of Appendix 2.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by observational studies.

Health technology assessments

Quebec's health technology agency (Agence D'Évaluation des Technologies et des Modes D'Intervention en Santé) published a health technology assessment on BAHA in 2006.[3] A summary was available in English.

The authors concluded that patients with BAHA experienced acoustic and non-acoustic benefits, especially for users of bone-conduction hearing aids and users of conventional hearing aids who suffer from chronic middle-ear infections. They also stated that limited evidence was found. The benefits were especially noted for users of BAHA and those with conventional hearing aids with chronic middle-ear infections. Other etiologies of hearing such as unilateral sensorineural hearing loss, bilateral implantation, and tinnitus were considered experimental patient indications. The authors reported that the technology was considered safe with most of the adverse events being skin reactions.

The included studies for the health technology assessment appeared to be three reviews (no statement regarding the methodological rigour of the reviews), including one from the Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care and twenty primary studies published after the Ontario review.

Systematic reviews and meta-analyses

Johnson, et al.[6] conducted a systematic review on the quality of life benefits of BAHA compared to bone-conduction hearing aids, air-conduction hearing aids, or no hearing aids. Non-acoustic benefit was measured through generic health-related quality of life outcomes and disease specific quality of life outcome measures.

Seven observational studies (n = 439) were included. Sample sizes ranged between nine and 227. The studies included a wide range of populations including children and adults, patients with and without prior hearing aid use, and a variety of hearing loss etiologies. Study quality was assessed through seven questions that related to areas such as power calculations, inclusion/exclusion criteria, description of hearing aid fitting processes, and whether measures of hearing aid verification were reported. The data could not be pooled due to the heterogeneity across the studies in outcome measures, inclusion criteria, and inconsistently presented results.

Patients who were new hearing aid users reported statistically significant benefits on two non-acoustic (quality of life) measures, the Visual Analog Scale of the Glasgow Benefit Inventory and the Hearing Handicap Inventory for Adults. While patients also had greater scores on other aspects of the Glasgow Benefit Inventory, no statistical significance numbers were reported. For patients who were previous users of air-conducted hearing aids, there was a statistically significant decline in the Euro QOL-5D; for example, these patients were more depressed and anxious. Statistically significant improvement in disability and handicap scores of the Hearing Handicap Inventory were reported for BAHA patients who previously had air-conducted hearing aids and bone-conducted hearing aids. The Medical Outcome Study SF-36 measure did not show any quality of life benefits for the BAHA; no statistics were reported. Also, previous hearing aid users had better scores on the Glasgow Benefit Inventory, indicating perceived enhanced quality of life; no statistics were reported. The authors reported that the generic measure of quality of life (i.e., Euro QOL-5D and Glasgow Benefit Inventory) may not be

sensitive enough with regard to communication problems with these patients. There was no industry support reported for this study.

The authors concluded that there was limited empirical evidence regarding the non-acoustic benefits of BAHA compared to conventional hearing aids or no hearing aids and therefore, physicians should be cautious when advising patients on the non-acoustic benefits of the BAHA.

Prospective Observational studies

Linstrom et al.[7] published a study in 2009 that compared seven patients with unilateral complete or near complete deafness with the BAHA to 20 patients with normal hearing.

Patients in the BAHA group had adult-onset deafness and were on average 49.7 years old and patients in the comparator group were on average 33.5 years old. Patients were assessed on acoustic and non-acoustic outcomes at one month, six months, and 12 months. However, scores on the outcome measures were pooled across the time points as time-related changes were not found. Patients were assessed on acoustic outcomes through the Hearing-in-Noise for Speech Recognition test. The authors reported that the BAHA patients' acoustic performance was not similar to the patients with normal hearing; however, no statistics were reported. When adjusted for baseline performance, the aided BAHA group (BAHA system turned on) did not outperform the non-aided BAHA group (BAHA system turned off) for signal-to-noise speech recognition. Quality of life outcomes were assessed through the Abbreviated Profile of Hearing Aid Benefit tool as well as the Single-Sided Deafness Questionnaire. For the Abbreviated Profile of Hearing Aid Benefit, the aided BAHA group performed statistically significantly better on three of four subscales (background noise, ease of communication, and reverberation sections) as well as the global scale compared with the non-aided BAHA group. No difference was found for the aversiveness subscale. The BAHA median scores for the Single-Sided Deafness were such that the authors stated the BAHA had a positive impact; however, statistics were not reported.

The authors concluded that the BAHA group experienced significant benefits on the Hearing-in-Noise Speech Recognition test up to one year after the BAHA implantation. However, the authors also stated that use of the BAHA did not result in speech recognition in noise comparable to the group with normal hearing. Non-acoustic benefits were also seen in the patients with BAHA. Industry involvement was not reported.

In 2009, Yuen et al.[8] published a study on 21 patients who had successfully undergone BAHA surgery. They compared acoustic and non-acoustic outcomes when the BAHA was turned on and turned off. The included patients had unilateral severe to profound sensorineural hearing loss and speech discrimination score of less than 30%. Various etiologies of hearing loss such as congenital (n = 1), acoustic neuroma (n = 9), idiopathic sudden sensorineural hearing loss (n = 3), and mumps (n = 1) were included. Most of the patients were male (n = 13) and hearing loss duration ranged between four months and 59 years. The ages of the patients ranged between 33 years to 77 years of age.

Non-acoustic outcomes were measured by two surveys, the Abbreviated Profile of Hearing Aid Benefit and the Glasgow Benefit Hearing Aid Benefit Profile. Sixteen of the 21 surveys were returned. No statistical significance testing regarding The Glasgow Benefit Hearing Aid Benefit Profile was reported due to the large standard deviation and highly variable scores. The

Abbreviated Profile of Hearing Aid Benefit scores indicated benefits for the BAHA through statistically significant higher scores for ease of communication, background noise, reverberation, and aversiveness to sound. The acoustic outcomes were measured by a Hearing-in-Noise Test for speech recognition. A benefit was seen for the BAHA when the speakers were placed to the left and right of the patient's head. The benefit did not exist when the speakers were placed in front and back of the patient's head. All outcomes were measured three months after the surgery.

The authors concluded that the BAHA system improved speech reception threshold levels and that non-acoustic benefit was also reported. The authors stated that there were no competing interests and no industry funded was reported.

Hol et al.[9] published a study in 2005 on the use of BAHA in patients with unilateral inner ear deafness. The objective was to assess acoustic and non-acoustic outcomes.

Each of the 39 patients was fitted with a BAHA contralateral routing of sound hearing aid (CROS) on a headband and evaluated after a minimum of one month. Of the 39 patients, 30 agreed to undergo BAHA surgery. They had the BAHA CROS fitted six to eight weeks after surgery. Each patient was assessed without the hearing aid at the start of the study, at least one month after having the BAHA CROS fitted on a headband, four to six weeks after the CROS was fitted after the BAHA surgery, and lastly, by mail, at one-year following BAHA surgery.

Of the 30 patients who had surgery to implant the BAHA CROS, 29 were included for analyses. One patient was excluded due to the patient's mental inability to complete the outcome measures. The majority of the patients (n = 19) had undergone acoustic neuroma surgery prior to the study. Acoustic performance was measured through sound localization measurements and speech perception in noise. The authors reported that while the sound localization performance was significantly better than chance, the scores did not approach the same levels of people with normal binaural hearing; no statistics were reported. Non-acoustic outcomes were measured through the Abbreviated Profile of Hearing Aid Benefit; Glasgow Benefit Hearing Aid Benefit Profile; the International Outcome Inventory for Hearing Aids, Single-Sided Deafness Questionnaire. The results for the non-acoustic outcomes were generally positive.

The authors concluded that the BAHA CROS cannot restore binaural hearing in patients with unilateral inner ear deafness and that patients were satisfied with the BAHA CROS one year after surgery.

Limitations

Methodological rigour of the included studies was limited as non-randomized study designs are associated with higher risk of bias. However, RCTs may not be ethically or logistically possible for surgically implanted hearing aids. No studies for the CIC hearing aids were identified.

Outcomes were not measured past one year follow-up thus the acoustic and non-acoustic benefits for longer periods of time are unknown. In addition, the effectiveness of the BAHA under a wide range of environmental conditions (e.g., internationally, with use of helmets, interference with other electronics), durability of the hearing aids, and infection rates were not explored.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Limited evidence was identified regarding the acoustic and non-acoustic benefits of BAHA. The relevant included evidence was mainly observational studies which are associated with higher risk of bias. The health technology assessment from 2006 indicated that using BAHA for unilateral sensorineural hearing loss, bilateral implantation, and tinnitus were considered experimental patient indications. The authors of the systematic review indicated that due to the lack of evidence, caution should be used when advising patients on the non-acoustic benefits of the BAHA. None of the identified literature pertained to how BAHA would perform in environments that are not representative of typical day to day activities.

No evidence was identified for the CIC hearing aids. No relevant economic studies were identified for BAHA or CIC hearing aids.

No evidence was found that addressed the environmental demands of specific jobs, and therefore the applicability of the limited identified evidence should be considered when discussing possible treatments options with these patients.

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REFERENCES:

1. Cigna. *Cigna medical coverage policy: hearing aids* [Internet]. Philadelphia (PA): Cigna; 2008. [cited 2010 Feb 5]. Available from: http://www.cigna.ca/customer_care/healthcare_professional/coverage_positions/medical/mm_0093_coveragepositioncriteria_hearing_aids.pdf

2. ECRI Institute. *Bone-anchored hearing aid implants* [Internet]. In: HTAIS hotline service: custom reports. Plymouth Meeting (PA): ECRI Institute; 2007 [cited 2010 Feb 5]. Available from: http://www.ecri.org Subscription required.

3. *Bone-anchored hearing aids: summary* [Internet]. Montréal: Agence d' Évaluation des Technologies et des Modes d'Intervention en Santé; 2006. [cited 2010 Feb 4]. Available from: http://www.aetmis.gouv.qc.ca/site/en_publications_2006.phtml English summary.

4. Health Canada. *Medical Devices Active Licence Listing* [database on the internet]. Ottawa: Health Canada; 2007 -; 2010 [cited 2010 Feb 16]. Available from: http://webprod.hc-sc.gc.ca/mdll-limh/start-debuter.do?lang=eng

5. Abel SM. Barriers to hearing conservation programs in combat arms occupations. *Aviat Space Environ Med.* 2008 Jun;79(6):591-8.

6. Johnson CE, Danhauer JL, Reith AC, Latiolais LN. A systematic review of the nonacoustic benefits of bone-anchored hearing AIDS. *Ear Hear.* 2006 Dec;27(6):703-13.

7. Linstrom CJ, Silverman CA, Yu GP. Efficacy of the bone-anchored hearing aid for single-sided deafness. *Laryngoscope.* 2009 Apr;119(4):713-20.

8. Yuen HW, Bodmer D, Smilsky K, Nedzelski JM, Chen JM. Management of single-sided deafness with the bone-anchored hearing aid. *Otolaryngol Head Neck Surg.* 2009 Jul;141(1):16-23.

9. Hol MK, Bosman AJ, Snik AF, Mylanus EA, Cremers CW. Bone-anchored hearing aids in unilateral inner ear deafness: an evaluation of audiometric and patient outcome measurements. *Otol Neurotol.* 2005 Sep;26(5):999-1006.

10. *FAQs* [Internet]. In: EQ-5D: a standardised instrument for use as a measure of health outcome. Rotterdam: EuroQol Group; 2010 [cited 2010 Feb 25]. Available from: http://www.euroqol.org/eq-5d/faqs.html.

11. Mace AT, Isa A, Cooke LD. Patient quality of life with bone-anchored hearing aid: 10-year experience in Glasgow, Scotland. *J Laryngol Otol.* 2009 Sep;123(9):964-8.

12. Stein JM, Fickl S, Yekta SS, Hoischen U, Ocklenburg C, Smeets R. Clinical evaluation of a biphasic calcium composite grafting material in the treatment of human periodontal intrabony defects: a 12-month randomized controlled clinical trial. *J Periodontol.* 2009 Nov;80(11):1774-82.

13. Huch JL, Hosford-Dunn H. *Inventories of self-assessment measurements of hearing aid outcome* [Book chapter on the Internet]. 2nd ed. In: Sandlin RE, editor. Textbook of hearing aid amplification. San Diego (CA): Singular Publishing Group Thomson Learning; 2000 [cited 2010 Feb 25]. Available from: http://books.google.com/books?id=MZDu1Sti69kC&pg=PA502&lpg=PA502&dq=HHIA+Newman&source=bl&ots=89pozQlULD&sig=YyXS0e82tYf7Ofg3kjJlSk0v9l0&hl=en&ei=96iGS__pBtWUtgfp5MGgDw&sa=X&oi=book_result&ct=result&resnum=2&ved=0CAwQ6AEwAQ#v=onepage&q=HHIA%20Newman&f=false.

14. Mental Health Statistics Improvement Program Policy Group. *The medical outcomes study 36-item short-form health survey* [Internet]. Rockville (MD): National Institute of Mental Health; 2004. [cited 2010 Feb 25]. Available from: http://www.mhsip.org/reportcard/sf36.pdf

APPENDIX 1: Definitions of Non-Acoustic Measures

Abbreviated Profile of Hearing Aid Benefit[9]
The questionnaire has four domains: ease of communication, listening under reverberant conditions, listening in background noise, and aversiveness to sound. There are 24 items and a higher score on specific domains are indicative of hearing problems.

Euro QOL-5D [6,10]
A two-part instrument. The first is a questionnaire that provides measures on the following health domains: usual activities, mobility, self-care, pain/discomfort, utility, and anxiety/depression. The second part is a Visual Analog Scale with 100 being best imaginable health and 0 being worst imaginable health.

Glasgow Benefit Inventory[11,12]
This tool is used to assess a patient's quality of life after a medical intervention. There are 18 questions each based on a five-point Likert scale. There are twelve questions that address general factors, three questions that address social support, and three questions that address physical health. There are two parts, the first covering four predetermined environments and the second part allows patients to choose four additional situations where they experience hearing difficulties.

Hearing Handicap Inventory for Adults[13]
A 25-item questionnaire that identifies problems that hearing loss may be causing for the patient. The two subscales are emotional reaction and perceived social limitations. The maximum score is 100 and the minimum score is 0; with a higher score representing a higher perceived handicap. Patients respond "Yes" (four points), "No" (zero points), or "Sometimes" (two points).

International Outcome Inventory for Hearing Aids[9]
A seven–item survey that asks hearing aid users about the hours per day they use the hearing aid, the benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others, and quality of life. Each question is based on a five-point scale with a higher score indicative of a better outcome.

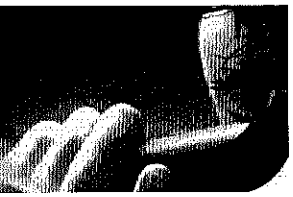
The Medical Outcome Study SF-36 [14]
This 36-item questionnaire measures health status over eight general health concepts including bodily pain, general health, vitality, social functioning, and mental health.

Single-Sided Deafness Questionnaire[9]
The questionnaire consists of 12 items regarding to the use, satisfaction, and benefit of using the hearing aid in different listening situations compared to no hearing aid. Each question is based on either a three-point or four-point scale. In addition, the aesthetics and handling of the hearing aid are also questioned and are answered on a discrete visual analogue scale; with a score of 10 indicating "very satisfied" and a score of 1 indicating "very dissatisfied".

APPENDIX 2: Additional Information for Included Studies

Table 1: Summary of Health Technology Assessments and Systematic Reviews for Bone-Anchored Hearing Aids

Study (Year)	Patient population, inclusion and exclusion criteria	Interventions compared (number of patients)	Outcomes	Number of included studies	Evaluated study quality?	Summary of main results
Health Technology Assessment						
AETMIS[3] (2006)	All ages, various etiologies of hearing loss	BAHA (sample sizes not reported)	Acoustic, non-acoustic	3 literature reviews, 20 clinical trials	Not reported	Benefits, mainly non-acoustic, by users of bone-conduction hearing aids and by users of conventional aids who suffer from chronic middle-ear infections Most complications are skin reactions Use in patients with bilateral implantations, unilateral sensorineural hearing loss, and tinnitus is considered to be experimental
Systematic Review						
Johnson, et al.[6] (2006)	All ages, various etiologies of hearing loss	BAHA (n = 439) versus more conventional hearing aids or no hearing aids	Non-acoustic: Generic health-related QOL measure or disease-specific QOL measure	7 observational	Yes	<u>New users of hearing aids</u> Glasgow Benefit Inventory showed increased quality of life, no statistical significance reported Hearing handicap Inventory for Adults, respondents with BAHA had statistically significant improvement (p = 0.04) <u>Experienced users of hearing aids</u> No differences for the Medical Outcome Study SF-36 questionnaire



Study (Year)	Patient population, inclusion and exclusion criteria	Interventions compared (number of patients)	Outcomes	Number of included studies	Evaluated study quality?	Summary of main results
						Respondents showed a significant decline ($p < 0.01$, effect size = 0.3) in the Euro QOL-5D, a generic quality of life measure, in those who had previous air-conduction hearing aids (e.g., more anxious, more depressed) Respondents of the Hearing, Handicap and Disability Inventory showed a significant reduction in disability ($p < 0.01$, effect size = 0.79) and handicap ($p < 0.01$, effect size = 0.86) after the BAHA fitting, for previous users of air-conduction hearing aids Respondents of the Hearing, Handicap and Disability Inventory had a significant reduction in disability($p < 0.01$, effect size = 1.42) and handicap ($p < 0.01$, effect size = 0.79) after the BAHA fitting, for previous users of bone conduction hearing aids.

AETMIS = Agence D'Evaluation Des Technologies et Des Modes D'Intervention En Santé; BAHA = bone anchored hearing aid; RCT = randomized control trial; QOL = quality of life

Table 2: Summary of Findings for Included Primary Studies

Study (Year)	Patient population, inclusion and exclusion criteria	Interventions compared, Number of patients	Patient traits	Study outcomes, Follow-up	Summary of main results
Linstrom, et al[7] (2009)	Unilateral complete or near complete deafness (adult-onset), normal or near-normal hearing in the better ear, between 18 years and 75 years Etiologies (each n = 1) Acoustic neuroma excision, idiopathic sudden sensori-neural hearing loss, excision of glomus jugulare, perilymph fistula, radical masoidectomy for cholesteatoma, failed surgery for otosclerosis; seventh patient's etiology not reported	BAHA, n = 7 Comparator (people with normal hearing), n = 20	Sex BAHA 2 males, 5 females Comparator 5 males, 15 females Mean age BAHA = 49.7 years (range: 353 years to 66.7 years) Control = 33.5 years (range: 22.7 years to 70.4 years) Length of deafness Mean: 7.39 years (range: 2 years to 14 years)	Follow-ups occurred at 1 month, 6 months, 12 months Acoustic Hearing-in-Noise test for speech recognition Non-acoustic Abbreviated Profile of Hearing Aid Benefit; Single-Sided Deafness Questionnaire	Acoustic There were no statistically significant changes in signal-to-noise speech recognition performances for the BAHA group (aided and unaided), when adjusted for baseline performance The BAHA aided and unaided signal-to-noise speech recognition did not approximate the control group Non-acoustic For the Abbreviated Profile of Hearing Aid Benefit, the aided BAHA group experienced statistically significantly favourable scores on the listening in background noise ($p < 0.001$), ease of communication ($p = 0.0003$), listening under reverberant conditions domains ($p < 0.0001$), and the global scale ($p < 0.0001$). No difference was found for the aversiveness of sound domain ($p = 0.11$) For the Single-Sided Deafness Questionnaire, BAHA median responses indicated positive impact, no statistics reported.

Study (Year)	Patient population, inclusion and exclusion criteria	Interventions compared, Number of patients	Patient traits	Study outcomes, Follow-up	Summary of main results
					Time over the follow-up periods was not a statistically significant factor in either questionnaire
Yuen, et al.[8] (2009)	Unilateral severe to profound sensorineural hearing loss and speech discrimination score of less than 30 per cent Etiologies of hearing loss included congenital (n = 1), acoustic neuroma (n = 9), idiopathic sudden sensorineural hearing loss (n = 3), and mumps (n = 1)	n = 21 BAHA turned on and BAHA turned off	Age Range: 33 years to 77 years Sex 8 males 13 females Duration of deafness Range: 4 months to 59 years	Acoustic 3 month follow up: hearing-in-noise test for speech recognition Non-acoustic 3 month follow up: Abbreviated Profile of Hearing Aid Benefit; Glasgow Hearing Aid Benefit Profile	Acoustic Mean decrease in signal-to-noise ratio was 5.5 decibels SPL (range: 2 decibels to 11 decibels) when BAHA was turned on, p = 0.00001 for the 90/270 speaker paradigm Mean increase in single-to-noise ratio was 1.6 decibels SPL (range: 0 to decibels) for the 0/180 speaker paradigm when BAHA turned on (p = 0.01) Non-acoustic 16 of 21 returned surveys Abbreviated Profile of Hearing Aid Benefit: when BAHA turned on, ease of communication (change score = 16.2, 95%CI: 7.4 to 2.0), background noise (change score = 18.2, 95%CI: 9. to 26.9), and reverberation (change score = 26.4, 9 CI = 1.8 to 37.0), and aversiveness to sound (change score = 9.5 (95%CI: 0.4 to 18.). Glasgow Benefit Hearing Aid Benefit Profile: Large standard deviations in the scores

Study (Year)	Patient population, inclusion and exclusion criteria	Interventions compared, Number of patients	Patient traits	Study outcomes, Follow-up	Summary of main results
					revealed highly variable experiences with the BAHA
Hol et al.[9] (2005)	Unilateral inner ear deafness Etiologies of hearing loss: Acoustic neuroma surgery (n = 19); cerebellopontine tumour (n = 2), congenital unilateral deafness (n = 3), stapedotomy surgery (n = 2), Morbus Meniere (n = 1), trauma (n = 1), cholesteatoma surgery (n = 1), unknown origin (n = 1) One patient (acoustic neuroma) later excluded due to inability to complete the outcome questionnaires due to mental abilities	n = 30 Unaided Fitted with CROS hearing aid, evaluated after at least one month BAHA surgery and the BAHA CROS fitted six to eight weeks later, evaluated four to six weeks after the BAHA CROS fitting	Sex 14 female 15 male Age Range: 29 years to 79 years Time with hearing aid Range: 7 months to 79 years and 3 months	Acoustic Speech Perception Non-acoustic Abbreviated Profile of Hearing Aid Benefit; Glasgow Benefit Hearing Aid Benefit Profile: -unaided, conventional CROS, BAHA CROS at six weeks and one year follow up International Outcome Inventory for Hearing Aids, and Single-Sided Deafness Questionnaire: -with BAHA CROS at six weeks and one year follow up Independent assessor for all outcomes, except for the one-year follow-up for the BAHA CROS, via the mail All were the Dutch versions	Acoustic Patients with the BAHA CROS were able to localize sounds significantly better than chance, but the scores were not similar to than normal binaural hearing, no statistics reported. Non-acoustic Abbreviated Profile of Hearing Aid Benefit; Glasgow Benefit Hearing Aid Benefit Profile, at 6 weeks (change from baseline, p value) CROS: ease of communication (-7.2, p = 0.03), background noise (-21.1, p = 0.00), reverberation (-9.6, p = 0.0001), aversiveness to sound (12.7, p = 0.02) BAHA CROS: ease of communication (-13.1, p = 0.001), background noise (-21.1, p = 0.00), reverberation (-19.1, p = 0.00), aversiveness to sound (-3.7, p = 0.52) Glasgow Benefit Hearing Aid Benefit Profile, at 6 weeks Mean Benefit from baseline BAHA CROS: 52% CROS: 39% Mean Residual Benefit from baseline

Study (Year)	Patient population, inclusion and exclusion criteria	Interventions compared, Number of patients	Patient traits	Study outcomes, Follow-up	Summary of main results
				Mean follow up = 1 year, 4 months (range: 11 months to 2 years, 1 month	BAHA CROS: 32% CROS: 42% Mean satisfaction from baseline BAHA CROS: 51% CROS: 32% International Outcome Inventory for Hearing Aids, change between 6 weeks and 1 year BAHA CROS: six of seven domain scores did not differ significantly (n = 23); one domain, satisfaction, was statistically significantly poorer (p = 0.0017) Single-Sided Deafness Questionnaire BAHA CROS, quality of life improved in 21 of 24 patients who responded (timepoints not reported)

BAHA = bone-anchored hearing aid; CI = confidence interval; CROS = contralateral routing of sound

Bone-anchored hearing aids (BAHAs) for people who are bilaterally deaf

Bone-anchored hearing aids (BAHAs) for people who are bilaterally deaf: a systematic review and economic evaluation

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Executive summary

Health Technology Assessment 2011; Vol. 15: No. 26
DOI: 10.3310/hta15260

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

Executive summary

Background

A bone-anchored hearing aid (BAHA) consists of a permanent titanium fixture, which is surgically implanted into the skull bone behind the ear, and a small detachable sound processor that clips onto the fixture. Sound is transmitted to the cochlea via bone conduction. BAHAs are suitable for people with conductive or mixed hearing loss who cannot benefit fully from conventional hearing aids. They can be used unilaterally or bilaterally for people with bilateral hearing loss.

Objectives

- To assess the clinical effectiveness and cost-effectiveness of BAHAs for people who are bilaterally deaf. The evaluation will consider BAHAs compared with conventional hearing aids, ear surgery and the unaided condition, and the use of unilateral or bilateral BAHAs.
- To adapt an existing economic model or develop a new economic model relevant to the UK setting.
- To identify areas where further research is required.

Methods

Data sources

Nineteen electronic databases, including MEDLINE, EMBASE and The Cochrane Library, were searched from inception to November 2009. Bibliographies of relevant papers were checked and experts were contacted to identify additional studies.

Study selection

Titles and abstracts were screened for eligibility and inclusion criteria defined a priori were applied to the full text of selected papers by two reviewers independently. The inclusion criteria were as follows:

- Participants: adults or children with bilateral hearing loss.
- Interventions: BAHAs attached to a surgically implanted titanium fixture.
- Comparisons: unilateral versus bilateral BAHAs, conventional hearing aids [air conduction hearing aid (ACHA) or bone conduction hearing aid (BCHA)], unaided hearing, ear surgery (tympanoplasty, myringoplasty, ossiculoplasty, stapedectomy and stapedotomy).
- Outcomes: hearing measures, aided hearing thresholds, speech recognition scores, validated measures of quality of life (QoL) and patient satisfaction, adverse events, measures of cost-effectiveness [cost per quality-adjusted life-year (QALY); cost per life-year saved] and consequences for health-service resources.
- Types of studies:
  - Systematic review of clinical effectiveness – randomised controlled trials, controlled clinical trials, prospective cohort analytic studies (with control group), prospective cohort pre and post studies (one group, before and after BAHA surgery), cross-sectional 'audiological comparison studies' (one time point) and prospective case series. Only

studies with the most rigorous designs were included for each comparator. Where higher level evidence was limited to BAHA models no longer in current use, lower level evidence for models in current use was included. Abstracts were considered if sufficient information was presented.

- Systematic review of cost-effectiveness – full economic evaluations reporting both costs and outcomes were eligible. Conference abstracts were not eligible for inclusion in the cost-effectiveness section.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with differences resolved through discussion.

Data synthesis

Clinical effectiveness data were synthesised through a narrative review with full tabulation of results. Audiological outcome measures were discussed throughout the review of clinical effectiveness as reported by the included studies, including the use of descriptions such as 'improvement' or 'deterioration'. To aid interpretation of the data, lower hearing thresholds were considered to be 'better' than higher thresholds, but it is acknowledged that this is a simplistic approach and, although true in many cases, it is not necessarily so.

Results

Quantity and quality of studies

Searching identified 665 references; 41 of these met the inclusion criteria. After selecting the highest level of evidence available for each comparator and identifying additional studies with BAHA models in current use, 12 studies (reported in 15 publications) were included in the review of clinical effectiveness (seven cohort pre–post studies and five cross-sectional audiological comparison studies). No studies with a control group were identified. Seven studies compared BAHAs with conventional hearing aids, three of these and one additional study compared BAHAs with unaided hearing, and four studies compared unilateral and bilateral BAHAs. No prospective studies comparing BAHAs with ear surgery were identified. The overall quality was rated as weak for all included studies and meta-analysis was not possible due to differences in outcome measures and patient populations.

Summary of clinical effectiveness

BAHAs versus BCHA

Two studies found an improvement in sound field pure-tone average and warble-tone thresholds with BAHAs, but statistical analysis was reported by only one study ($p < 0.01$). One study found hearing was better with the BCHA at 0.25 and 0.50 kilohertz (kHz) [p-value not reported (NR)]. Studies reported improvements in 100% speech audiometry discrimination [62 decibels hearing level (dB HL) vs 48 dB HL], location of a sound (0% vs 80% of cases) and maximum phoneme score [mean standard deviation (SD) 36.1% (28.9%) vs 48.7% (31.7%)], but statistical significance was not reported. An improvement in speech reception threshold in quiet {mean difference 2.7 decibels (dB) (SD 4.4 dB), $p < 0.05$} and speech-to-noise ratio [2.5 dB (SD 2.2 dB), $p < 0.05$] was found in one study, but another study found no difference in speech recognition threshold {mean decibels A-weighted [dB(A)] (SD): 40 (7.1) vs 38.8 (11.1), p = NR}. No statistically significant difference in mean sound field speech discrimination score at 63 dB was found by one study. Statistically significant improvements in QoL were found with a disease-specific instrument but not with generic QoL measures in one study.

BAHAs versus ACHA

Results for sound field pure-tone or warble-tone thresholds were inconsistent between the studies; for example, one study found the ACHA produced better results between 1 and 4 kHz (p = NR), another found an improvement in mean thresholds (0.5–4.0 kHz, $p < 0.0.1$) with the BAHA. The direction of the effect was also unclear for speech audiometry. Three studies reported better outcomes with the ACHA for speech discrimination scores [mean (SD) 91.6% (14.7%) vs 84% (22.3%), p = NR], maximum phoneme score [mean (SD) 81.6% (8.7%) vs 67.6% (22.2%), p = NR] or speech recognition threshold [mean (SD) 39 dB(A) (10.8) vs 45 dB(A) (5), p = NR; mean deterioration with BAHA –6.4 dB (SD 3.7), $p < 0.05$]. One study found no difference in maximum phoneme score [difference 1.0% (SD 5.4%), p = not significant]. However, three studies found an improvement in speech-to-noise ratio with BAHA (difference range 1.1–2.5 dB). Speech discrimination score was statistically significantly better with the BAHA in the congenital group but not in the chronic suppurative otitis media group in one study. Statistically significant improvements in QoL were found with a disease-specific instrument but not with generic QoL measures in one study.

BAHAs versus unaided hearing

Of the four included studies, all found improvements in sound field thresholds with BAHA, which were statistically significant in the two studies reporting analysis. Three studies reported speech audiometry and found improvements with BAHAs compared with unaided hearing.

Unilateral versus bilateral BAHAs

An improvement in sound field average tone thresholds with bilateral BAHAs compared with unilateral BAHAs was found in adults (2–15 dB) and a small group (n = 3) of children [30 (SD 5) dB HL vs 25 (SD 5) dB HL].

Speech recognition thresholds in quiet were statistically significantly lower with bilateral BAHAs in two studies [41.5 dB(A) vs 37.5 dB(A); 38.7 dB HL vs 33.3 dB HL], although one study found similar results between unilateral and bilateral BAHAs. Three studies demonstrated that bilateral BAHAs produced better results than unilateral BAHAs when noise was presented from the baffle/best side (the side with the BAHA in the unilateral condition), but not when noise was presented from the shadow side (the side opposite to the BAHA in the unilateral condition); this is due to the increased noise transmitted to the ears with an extra BAHA on the shadow (noise) side. Three studies found that localisation of sound was improved with bilateral BAHAs. Two studies suggested that BAHAs enable binaural hearing. Similar results were found for unilateral and bilateral BAHAs on the Meaningful Auditory Integration Scale and Meaningful Use of Speech Scale and the International Outcomes Inventory for Hearing Aids for most items.

Adverse events

The included studies reported very limited data on adverse events. Five prospective case series reported rates of loss of implants ranging between 6.1% of implants (9–25 months' follow-up) and 19.4% of implants (median 6 years' follow-up). The vast majority of participants experienced no, or minor, skin reactions.

Summary of cost-effectiveness studies

Systematic searches identified no relevant, published full economic evaluations of BAHAs. One unpublished economic evaluation, with a minority of participants having bilateral hearing loss, was identified. Two cost studies were identified, one of which was used to help inform the cost analysis for the economic model. One QoL study was also identified, but on further inspection data were of limited value.

Summary of economic model

A decision-analytic model was developed to estimate the cost-effectiveness of unilateral BAHAs compared with BCHAs for a cohort of adults and children with hearing loss and who were ineligible for conventional ACHAs. The model was informed by a systematic search of the literature to identify parameters on the natural history and epidemiology for people with profound hearing loss, health-related QoL and costs. The intervention effects in terms of improvement in hearing and adverse events were derived from the systematic review of clinical effectiveness. The perspective of the analysis was that of the NHS and Personal Social Services. The model estimated the costs and benefits of unilateral BAHAs over a 10-year time horizon, applying discount rates of 3.5%. The outcome of the economic evaluation is reported as cost per case and cost per successful implantation.

The incremental cost per user receiving a BAHA, compared with BCHA, was £16,409 for children and £13,449 for adults. The cost per case successfully treated with a BAHA was estimated at £18,681 for children and £15,785 for adults, over a 10-year time horizon. In an augmented, exploratory analysis (inferring QoL gains using the hearing dimension of the Health Utilities Index-3) the incremental cost per QALY gained was between £55,642 and £119,367 for children and between £46,628 and £100,029 for adults for BAHAs compared with BCHA, depending on the assumed QoL gain and proportion of each modelled cohort using their hearing aid for ≥ 8 hours per day.

Caution should be taken with the interpretation of the results from the economic evaluation owing to the paucity of evidence on the benefits of the BAHAs, particularly the absence of any robust mapping between audiological benefits (reported in studies included in the review of clinical effectiveness) and overall impact on QoL. As a consequence, the results of the economic evaluation should be regarded as exploratory.

Sensitivity analyses

Deterministic sensitivity analyses suggested that the results of our cost analysis were generally robust to variation in the value of input parameters. The results were most sensitive to variation in the probability of re-operation (when implants lose bone integration), the cost of surgical implantation and, to a lesser extent, the probability of intolerable pain requiring removal of the BAHA fixture.

Deterministic sensitivity analysis of the exploratory cost-effectiveness model suggested that the results were generally robust to variation in input probabilities and cost. The greatest variation, in relation to these factors, was associated with initial failure of bone integration, failure of BAHA implantation due to intolerable pain, the probability of re-operation due to loss of bone integration, the cost of day surgery for implantation and the cost of components of the BAHA system. The results of the cost-effectiveness analysis were highly sensitive to the assumed proportion of people using their hearing aid for ≥ 8 hours per day, with very high incremental cost-effectiveness ratio values (in the range from £500,000 to £1,200,000 per QALY gained) associated with a high proportion of people using BCHA for ≥ 8 hours per day. More acceptable values (in the range from £15,000 to £37,000 per QALY gained) were associated with a low proportion of people using BCHA for ≥ 8 hours per day (compared with BAHA). In a threshold analysis, differences in the proportion of people using their hearing aid for ≥ 8 hours per day (for BAHA compared with BCHA) of between 30% and 40% for the lowest estimated utility gain from aided hearing, and between 15% and 18% for the greatest estimated utility gain from aided hearing, were required for BAHAs to be cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained.

Conclusions

The available evidence is methodologically weak and the results have a high risk of bias. As such, there is a high degree of uncertainty about the conclusions of this systematic review.

The findings suggest that hearing is improved with BAHAs compared with no hearing aid, and although there are audiological benefits of BAHAs when compared with conventional BCHAs, the audiological benefits of BAHAs when compared with ACHAs are less clear. Limited data suggest an improvement in QoL with BAHAs when compared with conventional aids, but there is an absence of evidence regarding other potential benefits, such as length of time the aid is able to be worn and improvement of discharging ears. The evidence suggests that there are some benefits of bilateral BAHAs compared with unilateral BAHAs. The results of our cost analysis demonstrate that BAHAs are significantly more costly than conventional BCHAs. The additional costs continue while individuals remain using their BAHA and are not restricted to the initial processes of surgical implantation and fitting of the BAHA sound processor. Our exploratory cost-effectiveness analysis of BAHAs versus BCHAs suggests that BAHAs are unlikely to be a cost-effective option where the benefits (in terms of hearing gain and probability of using of alternative aids) are similar for BAHAs and their comparators. The greater the benefit from aided hearing and, in particular, the greater the difference in the proportion of people using the hearing aid for ≥ 8 hours per day, the more likely BAHAs are to be a cost-effective option. The inclusion of other dimensions of QoL may also increase the likelihood of BAHAs being a cost-effective option.

Recommendations for further research

A national audit of BAHAs should be implemented to provide clarity on the many areas of uncertainty surrounding BAHAs. Further research into the non-audiological benefits of BAHAs, including QoL, is required. Good-quality trials are needed to establish the benefits of bilateral BAHAs compared with unilateral BAHAs in people who are bilaterally deaf.

Source of funding

This report was commissioned by the National Institute for Health Research Health Technology Assessment programme as project number 08/25/02.

Publication

Colquitt JL, Jones J, Harris P, Loveman E, Bird A, Clegg AJ, *et al.* Bone-anchored hearing aids (BAHAs) for people who are bilaterally deaf: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(26).

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/25/02. The contractual start date was in May 2009. The draft report began editorial review in April 2010 and was accepted for publication in September 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

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Bone anchored hearing aid and contralateral routing of signals in patients with unilateral hearing loss
[Benförankrad hörapparat]

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

HTA-centrum
Sahlgrenska Universitetssjukhuset
2011-11-28

Bone anchored hearing aid and contralateral routing of signals in patients with unilateral hearing loss
[Benförankrad hörapparat]

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Published December 2011
2011:42

Suggested citation: Joacim Stalfors, Radoslava Jönsson, Mehrnaz Zeitooni, Christina Bergh, Eva-Lotte Daxberg, Thomas Franzén, Ola Samuelsson.
Bone anchored hearing aid in patients with unilateral hearing loss [Benförankrad hörapparat]
Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centre; 2011. HTA-rapport 2011:42

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HTA-centrum

Summary of the Health Technology Assessment

Method and patient group

Profound unilateral hearing loss is a permanent sensorineural hearing deficit in one ear. It is caused by dysfunction of the cochlea or auditory nerve, and can be of congenital or acquired origin. The patients experience impaired ability in speech recognition and sound localisation, thus affecting communication and quality of life. Current rehabilitation is the hearing aid solution, contralateral routing of signals from the deaf side to the normal hearing ear (CROS). In recent years, the bone anchored hearing aid (BAHA) has been advocated as an advantageous alternative.

Question at issue

Is bone anchored hearing aid system better than contralateral routing of signals or no hearing device in patients with profound unilateral hearing loss with regard to speech recognition, hearing threshold, sound localization, and quality of life?

PICO

P = Adults and children with unilateral deafness (or hearing loss) and normal hearing on the other side

I1 = BAHA
C1 = CROS (Contralateral routing of signals)

I2 = BAHA
C2 = No hearing device

I3 = CROS
C3 = No hearing device

O = Speech recognition, Hearing threshold, Sound localization, Quality of Life

Studied risks and benefits for patients of the new health technology

The systematic literature search identified one randomized controlled trial (RCT) and two cohort studies evaluating speech recognition and sound localisation ability with BAHA and CROS. The studies did not show any outcome differences between BAHA, CROS or no treatment in terms of speech recognition or sound localisation. The level of evidence according to the GRADE system for BAHA being superior toCROS or no hearing device for unilateral profound hearing loss regarding the outcomes speech recognition and sound localisation is very low (GRADE ⊕).

Four studies evaluated the subjective benefit of BAHA and CROS, one RCT and three cohort-studies. The studies did not show any outcome differences between BAHA, CROS or no treatment. The level of evidence according to the GRADE system for BAHA being superior to CROS or no hearing device for unilateral profound hearing loss regarding the outcome subjective benefit is very low (GRADE ⊕).

No serious complications following surgical implantation of BAHA have been reported. The most common adverse effects and complications of BAHA surgery are postoperative skin reaction which varies between 3 –30 %, and implant loss which varies between 1- 14 %.

Ethical questions

Should an expensive technique be offered when the level of evidence of an advantageous effect of BAHA on important outcomes is so low?

Economical aspects

The annual cost is estimated to be 1 500 000 SEK if all patients with profound unilateral hearing loss, 15-20 per year in region Västra Götaland, were offered BAHA or CROS.

Which health technology or method will be assessed?

Bone anchored hearing aid in patients with unilateral hearing loss

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1e **Are there any conflicts of interest for the proposer or any of the participants in the work group?**

No.

Disease/disorder of Interest and Present Treatment

2a **Disease/disorder of interest and its degree of severity**

Single Sided Deafness (SSD) or profound unilateral hearing loss mean no functional hearing ability in one ear. It is a permanent functional deficit that affects communication, orientation and audition.

The unilateral hearing loss is due to a dysfunction in the cochlea or auditory nerve, i.e. a sensorineural hearing loss. It can be of congenital or acquired origin, due to malformation, disease or injury. Unilateral hearing loss can develop suddenly or in a progressive manner.

Patients with profound unilateral hearing loss often experience difficulties in sound

localisation, speech perception and recognition in noisy environments (Christensen 2010). Quality of life studies have reported significant disabling effects of this disorder (Gatehouse 2004, Borton 2009). Studies have also shown that children with unilateral hearing loss have lower academic and cognitive achievements, more behavioural problems, and a delayed language acquisition (Lieu 2010, Lieu 2004, Martinez-Cruz 2009).

- ☐ Risk of premature death
- ☐ Risk of permanent illness or damage, or reduced quality of life
- ☑ Risk of disability and health-related quality of life

2b Prevalence and incidence of the disease/disorder

Studies of prevalence and incidence of unilateral hearing loss are sparse and report conflicting results. Registration by ICD-10 is not possible to use for identification of these patient groups. Therefore, estimation has been made based on epidemiological studies, and a clinical database in Göteborg for rehabilitation of children with hearing impairment.

At Sahlgrenska University Hospital, a clinical database has been used to register children (0-18 years of age) with hearing rehabilitation needs since 15 years. According to the register, a total of 50 children with profound unilateral hearing loss and normal hearing in the contralateral ear are currently receiving rehabilitation services in the Göteborg area. Epidemiological calculations for the population aged 0-18 years in the Region Västra Götaland (n =340 000) yields a lowest incidence of 1.6 per 100 000 children. This incidence is in accordance with other reports (Vartiainen 1998, Mehl 2002).

In adults, profound unilateral hearing loss is typically caused by infections, trauma, acoustic neuromas, Ménière´s disease or cerebrovascular disease. It is more common with increasing age. However, there are no reliable epidemiological data regarding the incidence and prevalence of profound unilateral hearing loss in these patient groups.

After surgical removal of an acoustic neuroma, most patients will be deafened on the side of intervention. The number of patients undergoing acoustic neuroma surgery is 12-18 per year in the Region Västra Götaland.

There are no data with regard to development of unilateral deafness due to trauma or Ménière´s disease.

Based on the above-mentioned figures an estimation of the incidence of profound unilateral hearing loss in the Region Västra Götaland region yields a lowest estimated incidence of profound unilateral hearing loss of 5.8/100 000 per year (children: 10, adults: 30 sudden deafness, 15 acoustic neuromas, 5 trauma and 2 Ménière´s disease).

The prevalence is dependent on the cumulative incidence and increases with age. However, in the estimation of the prevalence of unilateral hearing loss the expected bilateral hearing decline with age (presbyacusis) also needs to be accounted for.

2c Present treatment of the disease/disorder in the outpatient setting/ inpatient setting.

Hearing aids for children and adults in the Region Västra Götaland are provided by the Habilitation & Health (H&H) Sevices. Provision of care includes prescription of CROS (contralateral routing of signal) or BAHA (bone anchored hearing aid) devices. It is important to point out that intervention by technical means is only one part of the hearing rehabilitation, and counselling and communication optimisation by educational support can also be of benefit for the patient with unilateral deafness.

The use of technical aids is dependent on the patient's needs and type of hearing loss. After audiological assessment the interventional team chooses together with the patients the type of hearing aid.

Patients with profound unilateral hearing loss who require hearing aids are first offered a trial period with the CROS system. If this test period comes out positive, the CROS system may be prescribed. In some patients BAHA is tested. If the test result is better than with the CROS, surgery for the BAHA is offered. The surgical procedure is performed in an inpatient or outpatient (i.e. day surgery) setting. Surgery can be done in local anaesthesia in adults, whereas most children will be operated on in general anaesthesia in a two-stage procedure.

Patients with CROS or BAHA devices need follow-up visits to audiologists in secondary health care services for adjustments, service, reparation and re-prescription. For patients with BAHA, follow-up visits to surgeons at outpatient Otorhinolaryngology clinics are also necessary.

2d Number of patients per year who undergo current treatment regimen?

From databases and registries at the Habilitation and Health Services and the four Departments of Otorhinolaryngology in Region Västra Götaland, the CROS and BAHA-users can be identified.

During the 5-year period of 2006-2010, a total of 27 CROS devices were prescribed for children, all from the Göteborg area. The number of prescriptions for CROS to adults was 160 in Västra Götaland. However, these numbers include both first-time prescriptions as well as re-prescriptions of CROS.

A total of 326 BAHA fittings were performed during 2006-2010 for children and adults. The majority of BAHA operations was performed at Sahlgrenska University Hospital, see table below.

Care provider in Västra Götaland	Paediatric	Adult
NU Hospital group	0	16
Skaraborg Hospital	0	1
Sahlgrenska University Hospital	45	129
Southern Älvsborg Hospital	0	0

2e The normal pathway of a patient through the health care system

See figure 1 in the appendix for a graphical presentation of current pathways.

Most children with profound unilateral hearing loss are identified by hearing screening procedures at birth, in pre-school or in elementary school. Also, some children are referred due to their parents´ awareness or by established clinical guidelines for specific diseases.

Children younger than 5 years need special audiological procedures that are only available at four hospitals in the Region Västra Götaland. After the diagnosis has been established, habilitation services are initiated for these children with unilateral hearing impairment. The team services are multi-professional and include medical follow-up, educational intervention by specialists, and, whenever possible, the use of hearing aids or other technical aids. For the children under the age of one year, the Region Västra Götaland has special clinical guidelines for intervention services. (Andersson e et al). These can also be adhered to children and adolescents.

Adult patients most often contact the primary health care system due to sudden or progressive unilateral hearing loss. The patients will then be referred to a Department of Otorhinolaryngology for diagnostic work-up and/or treatment. Audiological assessments are performed by the Hearing & Deafness organisation.

There are no specific regional or national guidelines for rehabilitation of adults with profound unilateral hearing loss.

2f Actual wait time in days for medical assessment /treatment

All health care providers within Otorhinolaryngology offer a visit for medical assessment of suspected unilateral deafness within 90 days after referral.

The Habilitation and Health organisation reports audiological assessments and hearing aid fittings of all patients within 90 days after referral.

BAHA surgery is performed within 90 days after patient agreement.

Present Health Technology

3a Name/description of the health technology at issue

Contralateral routing of signals - CROS

The traditional hearing aid solution for patients with profound unilateral hearing loss and normal hearing in the other ear has been contralateral routing of signals, CROS (Harford & Barry 1965). With a CROS device, the sound is transmitted from the deaf side to the normal hearing ear. This is done by the use of a hearing aid microphone on the deaf ear and a cord or a wireless FM transmission that present the auditory signals to the amplifier on the normal ear. In the normal ear an open ear mould is inserted in the ear canal. Hereby, the system transmits sound energy from the deaf side by air conduction through the external ear canal, eardrum and the middle ear ossicles of the normal ear to the normally functioning cochlea and auditory system of the hearing side.

Bone anchored hearing aid - BAHA

A bone anchored hearing aid transfers sound by bone conduction. The sound processor is anchored to the temporal bone by a titanium implant that needs to be surgically installed. The specially designed transducer creates vibrations that are transmitted via the bone of the skull to the cochleae and sound is perceived.

Before surgery, the effect of a BAHA can be simulated and tested by transcutaneous stimulation when the system´s hearing aid is pressed by a softband against the skull.

At surgery the BAHA implant (3 or 4 mm long) is placed in the temporal bone and penetrates the skin after the removal of soft tissues. Normally the surgical procedure takes less than 60 minutes. After healing, the transducer is attached to the implant. The BAHA is worn on the deaf side and transmits sound via bone conduction to the contralateral normal functioning cochlea.

Both the CROS and BAHA devices compensate the head shadow effect and, thus, may improve speech intelligibility in noise, and ease of listening. Complete restoration of directional hearing cannot be achieved since input from two cochleae is required for normal sound localisation. Both techniques are well established for transmission of amplified sound, and are used clinically.

3b The work group's understanding of the potential value of the health technology

Patients with unilateral profound hearing loss often have severe problems to communicate in challenging listening conditions. With an appropriate hearing aid it may be possible to compensate for sounds from the deaf side, and, thereby, improve speech reception and recognition in certain situations. Positive benefit of hearing aids has been reported by disease-specific quality of life questionnaires with regard to communication, hearing in background noise, and in reverberation, in patients with unilateral hearing loss.

Today, many of these patients are offered a CROS device. However, this aid is seldom

preferred by the patient due to inconvenience. In many countries, a BAHA is offered as an alternative hearing aid.

Most probably, the majority of patients with unilateral profound hearing loss in Region Västra Götaland have no hearing aids. Patients with such hearing disabilities and challenging communication needs, should be offered test periods with both the CROS and the BAHA devices. It is likely that many patients will find one of these devices beneficial for their hearing demands. Thus, most probably many patients in the Region Västra Götaland could be better rehabilitated and achieve a higher quality of life. With the standards in practice today in Västra Götaland, patients are rehabilitated neither optimally nor equally.

3c The central question for the current HTA project in one sentence

Is bone anchored hearing aid system better than contralateral routing of signals or no hearing device in patients with profound unilateral hearing loss with regard to speech recognition, hearing threshold, sound localization, and quality of life?

3d **PICO** (P= Patients, I= Intervention, C= Comparison, O=Outcome)

PICO

P = Adults and children with unilateral deafness (or hearing loss) and normal hearing on the other side

I1 = BAHA
C1 = CROS (Contralateral routing of signals)

I2 = BAHA
C2 = No hearing device

I3 = CROS
C3 = No hearing device

O = Speech recognition, Hearing threshold, Sound localization, Quality of Life

3e Key words

Unilateral hearing loss, hearing aids, bone conduction

4 Search strategy, study selection and references – appendix 3

During February, 2011, the library performed searches in PubMed, the Cochrane Library, EMBASE, CINAHL, PsycInfo and a number of HTA-databases. Reference lists of relevant articles were also scanned for additional references. A total of 193 articles were identified after removal of duplicates, of which 109 abstracts were excluded by the library. Another 46 articles were excluded by the library after having been read in full text. 35 articles, 1 systematic review and 2 HTA reports were sent to the work group for assessment. 15 of these articles are included in the report, 4 are controlled studies and have been critically appraised.

The appraisal of articles is based on checklists from SBU regarding randomized controlled trials and other checklists developed by Olle Nyrén, professor, Karolinska Institutet, Stockholm,

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in appendix 3. The literature search and exclusion of abstracts were made by two librarians (TF, ELD) in consultation with the HTA-centre and the work group.

5a Describe briefly the present knowledge of the health technology

Speech recognition

The systematic literature search identified one randomised, controlled trial (RCT) and two non-randomised, controlled cohort studies reporting the effect on speech recognition with BAHA and CROS. All studies had serious limitations in study quality and uncertain external validity. The total number of patients in these studies was 77.

No differences were observed when BAHA, CROS or no hearing aid were compared with each another.

The level of evidence according to the GRADE system for BAHA being superior to CROS or no hearing device for unilateral profound hearing loss regarding the outcome speech recognition is very low (⊕).

Sound localisation

The three studies mentioned above also reported the effect on the ability to localise sound.

No differences were observed when BAHA, CROS or no hearing aid were compared with each another.

The level of evidence according to the GRADE system for BAHA being superior to CROS or no hearing device for unilateral profound hearing loss regarding the outcome sound localization is very low (⊕).

Quality of Life (Subjective experience)

The systematic literature search identified four studies that reported the subjective experience of BAHA or CROS devices. One was a randomised, controlled trial and three were non-randomised, controlled cohort-studies. All studies had serious limitations in study quality and uncertain external validity. The total number of patients was 392.

No differences in the subjective appreciation of a beneficial effect were observed when BAHA, CROS or no hearing aid were compared with each another.

The level of evidence for a subjective benefit of BAHA compared to CROS or no hearing device in patients with profound unilateral hearing loss is very low (GRADE ⊕).

Complications
In the analysis of complications to BAHA-surgery, only studies with more than 30 patient series were included. The majority of the patients in these studies were operated on for other indications than profound unilateral hearing loss. The rate and type of complications can be applied also on the present indication of profound unilateral hearing loss.

Early complications, such as necrosis of the skin around the implant, occurred in less than 1 % of the patients. Skin reactions around the implant, loss of osseointegration or implant failure, were the most commonly reported late complications. Adverse skin reactions were documented in 3 % - 30 % of the patients. Most skin reactions could be handled with local care, but the need of revision surgery was reported in up to 22 % of all cases. Lost osseointegration, and, as a consequence, a loosened? lost?implant, was reported in 1 - 14 %. A lost implant could be re-installed, but it requires additional surgical procedure.

The probable reasons for the different complication rates in various case series are the use of different surgical techniques, and variations of skin care around the implant performed by the patient and/or caregivers.

It can be concluded that BAHA is an established and relatively safe surgical procedure, and the complications associated with the implantation are not severe.

5b **Outcome tables** – appendix 1

5c **Excluded articles** – appendix 2

5d **Ongoing research**

No randomised, controlled or non-randomised controlled study with relevance to the question at issue of this HTA-report was identified in www.clinicaltrials.gov.

All BAHA patients at the large BAHA-center in Nijmegen, The Netherlands, are prospectively followed and results will be published.

A Polish national quality register of patients who have received BAHA was started in 2009. It has been reported that 18 % of the patients treated with BAHA had unilateral profound hearing loss as the indication for the procedure. More data are expected to be reported from this database.

6 Which medical societies or health authorities recommend the new health technology?

Bone anchored hearing aids for patients with unilateral profound hearing loss are reimbursed in many European countries such as the UK, Poland, The Netherlands, Belgium, Denmark and Switzerland.

In 2002 the Food and Drug Administration (FDA) approved the BAHA produced by the Cochlear company (previously Entific AB) for use in patients older than five years with unilateral hearing loss. In 2009 the BAHA of the Oticon Medical company was also approved. It has since then been reimbursed on the indication unilateral profound hearing loss within the American health insurance system. More than 50 % of the BAHAs in the USA are fitted for the unilateral profound hearing loss indication.

In Sweden, there are presently no national guidelines with regard to BAHA.

Ethical aspects

7a Ethical consequences

Given the very low level of evidence of the any beneficial effect of BAHA or CROS for profound unilateral hearing, an introduction of both techniques can be questioned. However, in the modern society with increasing demands on communication, some patients will most probably experience a better quality of life with BAHA or CROS.

7b Will other patient groups or other treatments be adversely affected (pushed aside) due to an introduction of the new health technology?

A systematic rehabilitation of patients with unilateral profound hearing loss would increase the prescription of BAHA and CROS. Without increase in resources, this could be disadvantageous for patient groups with other hearing impairments. A more efficient clinical pathway could to a certain degree compensate these consequences.

Organisation

8a When can this new health technology be put into practice?

The BAHA and CROS are already used in some patients with profound unilateral hearing loss, and also for other indications.
A structured rehabilitation program with both devices can be put into practice without delay.

8b Is this technology used in other hospitals in Region Västra Götaland?

Surgical implantation of BAHA is performed at three hospitals in the Västra Götaland region. More than 90 % of all the BAHA implants are currently performed at Sahlgrenska University Hospital. Both CROS and BAHA hearing devices are presently prescribed within the Hearing & Deafness centres in the region.

8c According to the work group, will there be any consequences of the new health technology for personnel?

New routines for patient information need to be implemented as well as tools for patient selections. Information of a structured rehabilitation program for children and adults with profound unilateral hearing loss needs to be communicated to professionals working within audiology.

8d Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Western Region of Sweden?

An increased volume for BAHA surgery would require additional resources for anaesthesia of children and some adults. Most probably a large proportion of surgeries could be performed in day-care, thus, resources can be used more efficiently.

Economy

9a Present costs of currently used technologies and the new technology

An estimation of the costs for BAHA and CROS has been performed and is presented below. Data on the number of surgeries, hearing device prescriptions and direct medical costs have been retrieved from regional computerised administrative systems. Data on surgeries and thus direct medical costs are judged as accurate. Data on hearing prescriptions are not valid, since data have not been registered consistently in the region.

In Region Västra Götaland approximately 180-190 patients were fitted with a CROS-device and 7 patients with a BAHA due to profound unilateral hearing loss and normal hearing in the contralateral ear during 2006 - 2010.

The table presents the number of fittings for BAHA and CROS-devices and the estimated costs.

	TOTAL	FyrBoDal/NU	Göteborg HDV/SU	Skaraborg	S Älvsborg
CROS-device No. of fittings for unilateral deafness	**186 (estimation)**	**no data**	**111**	**25**	**25**
Estimated cost per device	SEK 4 500 excl VAT				
Estimated cost for personnel per fitting	SEK 3 500				
Total cost	SEK 8 000				
No. of BAHA surgeries for unilateral deafness	**7 adults**	**0 children 1 adult**	**0 children 6 adults**	**0 0**	**0 0**
Estimated cost per surgical intervention	Day surgery: SEK 18 000 In-hospital surgery: SEK 26 000	Day Surgery: SEK 14 500	Day Surgery: SEK 18 100 In-hospital surgery: SEK 26 000	No data	-
Estimated cost per device	SEK 31 400				
Estimated cost personnel per fitting	SEK 4 400				
Total cost- Day surgery In-hospital surgery	 SEK 53 800 SEK 61 800				

9b **Total change of costs**

Given that 60 new patients develop profound unilateral hearing loss yearly, it can be anticipated that about one third of these patients would choose technical rehabilitation with CROS or BAHA (Hol 2010). Final prescription would be for only one of these devices. Thus, the maximal estimated cost corresponds to the cost for BAHA, but since some patients would choose the CROS the cost will be lower.

The estimated cost for 20 new CROS-patients is 160 000 SEK.
If BAHA were offered to 20 new patients, the total cost would be between 1 200 000 SEK.

For patients with a long history of profound unilateral hearing loss, a time-dependent higher demand for rehabilitation services can be anticipated. This number of patients is difficult to estimate, but may be between 15-30 per year over a four-year period, corresponding to an additional annual cost of 120 000 – 240 000 SEK (CROS) or 900 000 – 1 800 000 SEK (BAHA) respectively during this period.

Costs for re-prescriptions of hearing devices and handling of surgical complications have not been calculated in this HTA-report.

The annual cost of a structured rehabilitation program for profound unilateral hearing loss during the first four years is estimated to be up to 400 000 SEK (160 000 + 240 000; see above) if all patients receive CROS. If all patients are treated with BAHA the corresponding cost is estimated to be up to 3 000 000 SEK (1 200 000 + 1 800 000; see above).

9c **Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?**

No.

9d **Are there any available analyses of health economy? Cost advantages or disadvantages?**

No health economic studies have been published of BAHA in patients with unilateral hearing loss. A cost-effectiveness analysis on the use of BAHA used for all indications has recently been published. The study has been performed in Birmingham, UK.For all indications, of which unilateral deafness is one, the average cost per QALY (Quality Adjusted Life Year) was estimated to be £17 610 (this corresponds to 180 000 SEK). The threshold at which treatment is considered cost-effective by the National Institute for Health and Clinical Effectiveness is £ 20 000-30 000 (Monksfield 2011).

Unanswered Questions

10a Important gaps in scientific knowledge?

Well designed RCTs of the efficacy of BAHA and CROS are still lacking.

One hypothesis is that patients in need of audibility in noisy environments, especially when sound is presented to the deaf side, will benefit (such as taxi/bus drivers, teachers, and other professionals with special communication needs) by BAHA or CROS. However, studies in these subcategories of subjects with unilateral hearing loss are also lacking.

10b Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?

Yes.

1. An epidemiological study with the purpose to clarify the true incidence of unilateral severe and profound sensorineural hearing loss in children and adults.
2. A prospective, observational cohort study with the aim to identify the patients with greatest demands of hearing rehabilitation and to assess their functional outcome.
3. A randomised, controlled trial comparing the outcome of different hearing aids for the studied indication.

Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

Benförankrad hörapparat hos patienter med ensidig dövhet

Frågeställning:
Är ett benförankrat hörselhjälpsystem bättre än ett hjälpmedel med kontralateral ljudöverföring eller inget hörselhjälpmedel alls avseende taluppfattning, hörseltröskel, lokalisering av ljud och livskvalitet hos patienter med uttalad unilateral hörselnedsättning?

PICO

P = Vuxna och barn med ensidig dövhet och normal hörsel på andra sidan

I1 = Benförankrat hörselhjälpsystem (BAHA= boneanchored hearing aid)
C1 = Kontralateral ljudöverföring (CROS = Contralateral routing of signals)

I2 = BAHA
C2 = Inget hörselhjälpmedel

I3 = CROS
C3 = Inget hörselhjälpmedel

O = Taluppfattning, hörseltröskel, lokalisering av ljud, livskvalitet

Resultat av HTA-processen:

Metod och målgrupp:
Patienter med en permanent sensorineural hörselskada på ena örat har en uttalat nedsatt hörsel på den aktuella sidan. Detta leder till en nedsatt förmåga att korrekt uppfatta det talade språket och att lokalisera ljud. Idag rehabiliteras dessa patienter med hörselhjälpmedel som leder ljudsignaler från den skadade sidan över till det friska örat (s.k. CROS). Under senare år har en benförankrad hörapparat (s.k. BAHA) utvecklats och framförts som ett alternativ i behandlingen av danna patientgrupp.

Evidensläge:

Taluppfattning
Den systematiska litteratursökningen identifierade en randomiserad, kontrollerad studie (RCT) och två icke-randomiserade, kontrollerade observationsstudier som har rapporterat effekterna av BAHA och CROS avseende förmågan att uppfatta talat språk. Alla studierna hade allvarliga begränsingar i studiekvalitet och extern validitet. Inga skillnader förelåg när BAHA, CROS eller inget hörselhjälpmedel alls jämfördes med varandra.
Avseende taluppfattning är det vetenskapliga underlaget otillräckligt för att bedöma om BAHA är bättre än CROS eller inget hörhjälpmedel alls (GRADE ⊕).

Lokalisera ljud
Samma studier som rapporterat effekterna på taluppfattning har även redovisat sina resultat avseende förmågan att korrekt lokaliser ljud. . Inga skillnader förelåg när BAHA, CROS eller inget hörselhjälpmedel alls jämfördes med varandra.
Avseende förmåga att lokalisera ljud är det vetenskapliga underlaget otillräckligt för att bedöma om BAHA är bättre än CROS eller inget hörhjälpmedel alls (GRADE ⊕).

Livskvalitet (Subjektiva upplevelser)
Den systematiska litteratursökningen identifierade fyra studier som har rapporterat effekterna av BAHA och CROS med avseende på patienternas subjektiva upplevelser. En studie var en randomiserad, kontrollerad studie (RCT) och tre var icke-randomiserade, kontrollerade observationsstudier. Alla studierna hade allvarliga begränsningar i studiekvalitet och extern validitet. Inga skillnader förelåg när BAHA, CROS eller inget hörselhjälpmedel alls jämfördes med varandra.
Avseende livskvalitet är det vetenskapliga underlaget otillräckligt för att bedöma om BAHA är bättre än CROS eller inget hörhjälpmedel alls (GRADE ⊕).

Komplikationer och biverkningar:
Tidiga komplikationer som hudnekros runt implantatet av den benförankrade hörapparten inträffade hos mindre än 1% av alla patienter som fått en BAHA inopererad (oavsett indikation). Sena hudkomplikationer runt implantatet har rapporterats hos 3 – 30 % av alla patienter som erhållit BAHA. Frekvensen av fall där implantatet lossnar från sin benförankring eller helt upphör att fungera av annat skäl varierar mellan 1 – 14 %, och behovet av kirurgisk revision har rapporterats inträffa hos upp till 22 % av all patienter.

Etiska aspekter:
Ska en dyrt medicinskt hjälpmedel som benförankrad hörapparat erbjudas i rehabiliteringen när behandlingseffekterna är oklara och evidensläget är otillräckligt?

Ekonomiska aspekter
Kostnaden för ett strukturerat rehabiliteringsprogram i vilket alla patienter med ensidig dövhet behandlas med CROS beräknas till 400 000 kronor årligen under en fyra årsperiod. Om alla patienter i stället skulle behandlas med BAHA uppskattas den motsvarande årliga kostnaden till 3 000 000 kronor.

Sammanfattning och slutsats
Evidensläget avseende effekterna av benförankrad hörapparat hos patienter med ensidig dövhet avseende taluppfattning, lokalisering av ljud och livskvalitet är otillräckligt (GRADE ⊕).

För HTA-kvalitetssäkringsgruppen
Göteborg, Sverige, 2011-10-26

Christina Bergh, Professor

Denna HTA har genomförts på begäran av Hasse Ejnell, verksamhetschef, Verksamhet Öron- näs- och halssjukvård, Sahlgrenska Universitetssjukhuset.
En arbetsgrupp ledd av Joacim Stalfors, överläkare, Öron- näs- och halssjukvård, Sahlgrenska Universitetssjukhuset, Radoslava Jönsson, överläkare, Öron- näs- och halssjukvård, Sahlgrenska Universitetssjukhuset, och Mehrnaz Seitooni, audiolnom, Hörsel- och dövverksamheten, Habilitering och hälsa, Borås, har tagit fram rapporten.
Från HTA-centrum har professor Christina Bergh och docent Ola Samuelsson varit ansvariga, dessutom har Thomas Franzén, chef för Kliniska centralbiblioteket, Sahlgrenska Universitetssjukhuset, och bibliotekarie Eva-Lotte Daxberg deltagit i projektet.
HTA-rapporten och åberopad och förtecknad litteratur har sedan granskats av Karin Manhem, universitetslektor, Medicin, Sahlgrenska Universitetssjukhuset, samt Anders Larsson, överläkare, Neurologi, Södra Älvsborgs Sjukhus.

Slutsatser har diskuterats vid möten mellan HTA-centrum och HTA-projektgruppen. Ett utlåtande har tagits fram, diskuterats och fastställts vid HTA-kvalitetssäkrings-gruppens möte 2011-10-26
Projektet har pågått under perioden 2011-02-09—2011-10-26. Sista uppdatering av artikelsökning 2011-02-10

Statement from HTA-Centre, Region Västra Götaland

Bone anchored hearing aid in patients with unilateral hearing loss

Question at issue:
Is bone anchored hearing aid system better than contralateral routing of signals or no hearing device in patients with profound unilateral hearing loss with regard to speech recognition, hearing threshold, sound localization, and quality of life?
PICO

P = Adults and children with unilateral deafness (or hearing loss) and normal hearing on the other side

I1 = BAHA
C1 = CROS (Contralateral routing of signals)

I2 = BAHA
C2 = No hearing device

I3 = CROS
C3 = No hearing device

O = Speech recognition, Hearing threshold, Sound localization, Quality of Life

Summary of the health technology assessment:

Method and patient category:
Profound unilateral hearing loss is a permanent sensorineural hearing deficit in one ear. The patients experience impaired ability in speech recognition and sound localisation. Current rehabilitation is the hearing aid solution with contralateral routing of signals from the deaf side to the normal hearing ear (CROS). In recent years, the bone anchored hearing aid (BAHA) has been advocated as an advantageous alternative.

Level of evidence:

Speech recognition
The systematic literature search identified one randomised, controlled trial (RCT) and two non-randomised, controlled cohort studies reporting the effect on speech recognition with BAHA and CROS. All studies had serious limitations in study quality and external validity. No differences were observed when BAHA, CROS or no hearing aid were compared with each another.
The level of evidence according to the GRADE system for BAHA being superior to CROS or no hearing device for unilateral profound hearing loss regarding the outcome subjective benefit is very low (GRADE ⊕).

Sound localisation
The same three studies as above also reported the effect on the ability to localise sound. No differences were observed when BAHA, CROS or no hearing aid were compared with each another.
The level of evidence according to the GRADE system for BAHA being superior to CROS or no hearing device for unilateral profound hearing loss regarding the outcomes sound localisation is very low (GRADE ⊕).

Quality of Life (Subjective experience)
The systematic literature search identified four studies that reported the subjective experience of BAHA or CROS devices. One was a randomised, controlled trial and three were non-randomised, controlled cohort-studies. All studies had serious limitations in the study quality and uncertain external validity. No differences in the subjective appreciation were observed when BAHA, CROS or no hearing aid were compared with each another.The level of evidence according to the GRADE system for BAHA being superior to CROS or no hearing device for unilateral profound hearing loss regarding the outcome subjective benefit is very low (GRADE ⊕).

Side effects and complications:
Early complications, such as necrosis of the skin around the implant, occurred in less than 1% of the patients after implantation of a BAHA (regardless of the indication).
Late complications with skin reactions around the implant have been reported in 3 – 30 % of BAHA patients. The frequencies of loss of osseointegration or implant failure have varied between 1 – 14 %, and the need of revision surgery has been reported to occur in up to 22 % of all patients.

Ethical aspects:
Should an expensive technique be offered when the level of evidence of an advantageous effect of BAHA on important outcomes is so low?

Economical aspects
The annual cost of a structured rehabilitation program for profound unilateral hearing loss during the first four years is estimated to be up to 400 000 SEK if all patients receive CROS. If all patients are treated with BAHA the corresponding cost is estimated to be up to 3 000 000 SEK.

Concluding remarks
The level of evidence for a beneficial effect of bone anchored hearing aid to improve speech recognition, sound localization, and quality of life in patients with unilateral hearing loss is very low (GRADE ⊕).

On behalf of the Regional HTA Centre, Region Västra Götaland in Sweden
Göteborg, Sweden, 2011-10-26

Christina Bergh, Professor, MD.
Head of Regional HTA Centre,

The Regional Health Technology Assessment Centre (HTA-centrum) of the Western Region in Sweden (Region Västra Götaland, VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.
The Head of the Department of Otorhinolaryngology, Sahlgrenska University Hospital, Göteborg, Sweden, Hasse Ejnell requested the present HTA.
The HTA was accomplished during the period of 2011-02-07 – 2011-10-26. A working group under the chairmanship of Joacim Stalfors, MD, at the Department of Otorhinolaryngology, Sahlgrenska University Hospital, Göteborg, Sweden, produced the HTA report. The other members of the working group were Radoslava Jönsson, MD, Department of Otorhinolaryngology, and Mehrnaz Seitooni, Audiologist, Hearing & Deafness organisation, Habilitation & Health, Southern Älvsborgs Hospital, Borås, Sweden.
The participants from the HTA centre were Christina Bergh, MD, professor, Ola Samuelsson MD, PhD, Eva-Lotte Daxberg, librarian, and Thomas Franzén, Head of the Clinical Library, Sahlgrenska University Hospital, Göteborg, Sweden.
Anders Larsson MD, PhD, and Karin Manhem, MD, PhD, have critically appraised the report.

Table 1. Outcome variable: Speech perception/recognition.
CROS=Contralateral Routing Of Sound. BAHA = Bone-Anchored Hearing Aid. CIC = CROS device Completely In Canal.
SRT = Speech reception threshold expressed as dB Signal/Noise ratio. A lower SRT value corresponds to better performance.

Author, year	Country	Study design	Number of patients n=	With-drawals - dropouts	Result Control and interventions				Comments	Quality (may vary according to outcome)
Bosman et al. 2003	The Netherlands	Non-randomised, cross-over study	9	0	Unaided: SRT[i] Hearing side = -2.8 Deaf side = 1.8	CROS: SRT[i] Hearing side = -2.0 Deaf side = 0.5	BAHA: SRT[i] Hearing side = -3.5 Deaf side = 0.4		No statistical analysis performed. Authors concluded that CROS and BAHA "were equally successful".	Low
Hol et al. 2010b (Eur Arch Otorhino-laryngol)	The Netherlands	Randomised, cross-over study	10	2 CROS 1 BAHA 3 CIC	Unaided: SRT Hearing side = -4.3 Deaf side = 0.5	CROS: SRT Hearing side = -2.7 Deaf side = -1.7	BAHA: SRT Hearing side = -2.0 Deaf side = 0.4	CIC: SRT Hearing side = -4.6 Deaf side = 0.7	No statistical analysis performed. An observation was a trend of deteriorating SRT for CROS and BAHA when speech was presented to the ear with normal hearing.	Low
Martin et al. 2010	UK	Randomised. cross-over study	19		Difference in SRT between BAHA and Unaided: Speech and Noise in front: = - 0.4; p = 0.90 Speech front, Noise BAHA side: = - 5.3; p = 0.06 Speech front, Nose non-BAHA side: = 8.1; p = 0.06				The test with or without activated BAHA was performed on the same day.	Low

Footnote: i. Estimated from Figure 1 in the publication.

Table 2. Outcome variable: Subjective benefit.

CROS=Contralateral Routing Of Sound. BAHA= Bone-Anchored Hearing Aid. CIC = CROS device Completely In Canal.

APHAB = Abbreviated Profile of Hearing Aid Benefit questionnaire with four categories: EC = ease of communication. BN = background noise. RV = reverberation. AV = aversion. A lower score corresponds to a more favourable outcome.

SSQ = Speech, Spatial and Qualities hearing scale with three domains: SHRS = speech hearing rating. SRS = spatial rating. SQRS = sound qualities rating. A higher score corresponds to a more favourable effect.

Author, year	Country	Study design	Number of patients n=	With-drawals - dropouts	Result Control and interventions				Comments	Quality (may vary according to outcome)
Bosman et al. 2003	The Netherlands	Non-randomised, cross-over study	9	0	Unaided: APHAB EC = 16.7 BN = 67.6 RV = 37.7 AV = 32.3	BAHA: APHAB EC = 10.9 BN = 40.0 RV = 20.1 AV = 20.9	CROS: APHAB EC = 12.0 BN = 48.0 RV = 30.5 AV = 33.6		No statistical analysis performed.	Low
Hol et al. 2010b (Eur Arch Otorhino-laryngol)	The Netherlands	Randomised, cross-over study	10	2 CROS 1 BAHA 3 CIC	Unaided: APHAB EC = 28 BN = 60 RV = 45 AV = 35	BAHA: APHAB EC = 18 BN = 54 RV = 46 AV = 42	CROS: APHAB EC = 22 BN = 61 RV = 38 AV = 40	CIC: APHAB EC = 26 BN = 73 RV = 53 AV = 40	No statistical analysis performed.	Low
Martin et al. 2010	UK	Non-randomised, controlled observational study	54 BAHA 67 Controls	8 BAHA 18 Controls	Controls: SSQ[i] SHRS = 45 SRS = 33 SQRS = 67	BAHA: SSQ[i] SHRS = 50 SRS = 32 SQRS = 65			No significant differences between cases and controls.	Low
House et al. 2010	USA	Non-randomised, controlled observational study	126 BAHA 126 Controls	58 BAHA 65 Controls	Controls: SSQ[ii] SHRS = 5.3 SRS = 3.6 SQRS = 7.0	BAHA: SSQ[ii] SHRS = 5.7 SRS = 3.8 SQRS = 6.6			No significant differences between control and BAHA group on overall SSQ scores and subscales.	Low

i. The values represent the total sum of the entire subscale.

ii. The values represent the mean score of the entire subscale, estimated from Figure 1 in the publication.

Table 3. Outcome variable: Sound localisation.
CROS=Contralateral Routing Of Sound. BAHA = Bone-Anchored Hearing Aid CIC = CROS device Completely In Canal.
Sound lateralisation score presented as left/right in %. A score of 50% means that the lateralisation performance is equal to mere chance.

Author, year	Country	Study design	Number of patients n=	With-drawals - dropouts	Result Control and interventions				Comments	Quality (may vary according to outcome)
Bosman et al. 2003	The Netherlands	Non-randomised, cross-over study	9	0	Unaided: "At the level of chance"	CROS: "At the level of chance"	BAHA: "At the level of chance"		No data presented. No statistical analysis performed.	Low
Hol et al. 2010b (Eur Arch Otorhino-laryngol)	The Netherlands	Randomised, cross-over study	10	2 CROS 1 BAHA 3 CIC	Unaided: 500 Hz 54 % 3 000 Hz 61 %	CROS: 500 Hz 53 % 3 000 Hz 49 %	BAHA: 500 Hz 56 % 3 000 Hz 59 %	CIC: 500 Hz 53 % 3 000 Hz 70 %	No statistical analysis performed.	Low

Table 4. Complications in bone anchored hearing aid surgery.
SSD = Single-sided deafness

Author, year,	Country	Study group	Postoperative complication	Skin reactions	Revision surgery / longer abutment	Implant loss	New implant	Comment
de Wolf et al 2008	The Netherlands	n = 142 Follow-up 1-10.5 years (mean 5.6)		n = 40 (28.2 %)	Revision surgery n = 20 (14.1 %) Longer abutment n = 6 (4.2 %)	n = 14 (9.9 %)		3 SSD patients
House et al 2007	USA	n = 149 Consecutive patients 2001-2005 Follow-up No data	Wound infection n = 2 (1.3 %) Flap necrosis n = 1 (0.7 %)	Skin overgrowth n = 11 (7.4 %)	n = 11 (7.4 %)	n = 5 (3.4 %)	n = 3 (2.0 %)	127 SSD patients.
Hol et al 2010a (Annals of Otology…)	The Netherlands	n = 56 Follow-up No data	No data	No data	No data	n = 1 (1.7 %)		Patients with both congenital and aquired unilateral deafness.
Mace et al 2009	UK	n = 60 Surgery 1996-2006	No data	n = 17 (25.8 %)	Revision surgery n = 7 (10.6%)	n = 2 (3.0 %)	n = 2 (3.0%)	5 SSD patients
McDermott et al 2009	UK	n = 182 (230 implants) Follow-up 4-13 years Age <16 years 107 with significant medical history**	No data	n = 34 (18.7 %)	Revision surgery n = 14 (7.7 %) Longer abutment n = 15 (8.2 %)	n = 32 (17.6%) 25/32 lost implants were 3mm. Failure rate and age: <3 years: 40% 3-5: 38% 5-10: 8% >10 years: 1%	No data	No SSD patients
Reyes et al 2000	Sweden	n = 149 Follow-up 8 years	No data	Holger index for 149 patients: Grade >2 : n = 5 (3 %)	No data	n = 9 (6.0 %)	No data	No SSD patients
Shirazi et al 2006	USA	n = 58 Follow-up No data	Loss of skin graft n = 6 (10.3 %)	Skin overgrowth n = 3 (5.2 %)	Revision surgery n = 1 (1.7 %) Longer abutment n = 1 (1.7 %)	n = 2 (3.4 %)	n = 2 (3.4 %)	25 SSD patients

Table 4. Complications in bone anchored hearing aid surgery.
SSD = Single-sided deafness

Author, year,	Country	Study group	Postoperative complication	Skin reactions	Revision surgery / longer abutment	Implant loss	New implant	Comment
Van de Berg et al 2010	The Netherlands	n = 143 Follow-up 3-147 months	No data	Holger index for 143 patients: Grade >2 n = 16 (11,2 %)	n = 19 (13.3 %)	n = 3 (2.1 %)	n = 3 (2.1 %)	19 SSD patients.
Van Rompaey et al 2011	Belgium	n = 138 Follow-up 7-120 months (mean 61)	No data	Holger index for 82 patients: Grade >2 n = 24 (30 %) Skin overgrowth n = 19 (13.8 %)	n = 30 (22 %)	n = 9/82 (9 %)	No data	Number of SSD-patients not stated. Loose abutment reported in 20 patients (14.5 %).
Wazen et al 2008	USA	n = 218 (223 implants) Follow-up 4 -114 months (mean 44) Age 6-92 years, (mean 56)	n = 4 (1.8 %) Hematoma Abscess Bleeding Flap necrosis	Hypertrofic scar n = 10 (4.6 %) Dermatis n = 3 (1.4 %) Skin overgrowth n = 4 (1.8 %) Keloid formation n = 4 (1.8 %)	Revision surgery n = 10 (4.6 %) Longer abutment n = 1 (0.5 %)	n = 3 (1.4 %)	n = 3 (1.4 %)	114 SSD patients.
Welling et al. 1991	USA	n = 43 Follow-up up to 24 months Age 26-29 years, (mean 46)		Minor skin reaction: n = 19 (44 %) Need of flap revision: n = 1 (2.3 %)				

**Goldenhar syndrome, Treacher Collins syndrome, unusual chromosome deletions, Down syndrome, Pierre Robin syndrome, Turner syndrome, CHARGE syndrome.
SSD: singe sided deafness, or unilateral profound hearing loss.

Appendix 2

Study (author, publication year)	Reason for exclusion
Andersen 2006	Case series with less than 30 patients
Arndt 2010	Not the correct intervention
Bergeron 2006	Systemic review including only case series
Bovo 2011	Case series with less than 30 patients
Christensen 2010	Case series with less than 30 patients
CADTH 2010	Systematic review based on a limited literature search
Danhauer 2010	Systematic review of another patient category
Gluth 2010	Case series with less than 30 patients
Hol 2004	Case series with less than 30 patients
Hol 2005b (Audiol Neurotol)	Case series with less than 30 patients
Hol 2005a (Otology & Neurotol)	Case series with less than 30 patients
Kunst 2008	Case series with less than 30 patients
Lin 2006	Case series with less than 30 patients
Linstrom 2009	Not the correct comparison
McLarnon 2004	Case series with no data on complications reported

Appendix 2

Study (author, publication year)	Reason for exclusion
Niparko 2003	Case series with less than 30 patients
Ontario Health Technology Assessement series 2002	Systemic review including only case series
Pfiffner 2009	Case series with less than 30 patients
Priwin 2007	Not the correct patient category
Vaneecloo 2001	Case series with less than 30 patients
Wazen 2003	Case series with less than 30 patients
Wazen 2010	Case series with less than 30 patients
Yuen 2009	Case series with less than 30 patients

Appendix 3: Search strategy, study selection and references

Question(s) at issue:
Is bone anchored hearing aid system better than contralateral routing of signals or no hearing device in patients with profound unilateral hearing loss with regard to speech recognition, hearing threshold, sound localization, and quality of life?

PICO (P= Patients, I= Intervention, C= Comparison, O=Outcome)
The central question at issue includes three different comparisons, i.e. PICO 1 - 3

P = Adults and children with unilateral deafness (or hearing loss) and normal hearing on the other side

I1 = BAHA
C1 = CROS (Contralateral routing of signals)

I2 = BAHA
C2 = No hearing device

I3 = CROS
C3 = No hearing device

O = Speech recognition, Hearing threshold, Sound localization, Quality of Life
Quality of Life
Health care costs

Search strategy:

PubMed (2011-02-10)
bone-anchored hearing aid OR bone-anchored hearing aids OR baha OR Osseointegrated hearing aid OR Osseointegrated hearing aids OR CROS OR Contralateral Routing of Signals
AND
Hearing loss, unilateral OR ((unilateral OR one-sided OR single-sided) AND (deafness OR deaf OR hearing impairment))

90 results

The Cochrane Library (2011-02-10)
bone-anchored hearing aid):ti,ab,kw or (bone-anchored hearing aids):ti,ab,kw or (BAHA):ti,ab,kw or (osseointegrated hearing aid):ti,ab,kw or (Osseointegrated hearing aids):ti,ab,kw OR (CROS):ti,ab,kw or (Contralateral Routing of Signals):ti,ab,kw
AND
((unilateral):ti,ab,kw or (one-sided):ti,ab,kw or (single-sided):ti,ab,kw) AND deafness):ti,ab,kw or (deaf):ti,ab,kw or (hearing impairment):ti,ab,kw)) OR (hearing loss, unilateral):ti,ab,kw)

10 results

Cochrane reviews **0**
Other reviews **1**

Clinical trials **5**
Technology Assessments **4**
Economic evaluations **0**

EMBASE (OVID SP) (2011-02-10)
bone-anchored hearing aid.mp OR exp bone anchored hearing aid OR bone-anchored hearing aids.mp. OR BAHA.mp OR Osseointegrated hearing aid.mp. OR Osseointegrated hearing aids.mp. OR CROS.mp. OR Contralateral Routing of Signals.mp.
AND
unilateral hearing loss OR ((one-sided.mp. OR single-sided.mp. OR unilateral mp.) AND **(**deafness.mp. OR deaf,mp) OR exp hearing impairment))

101 results

CINAHL (EBSCO) (2011-02-10)
TX bone-anchored hearing aid OR TI bone-anchored hearing aids OR TX BAHA OR TX osseointegrated hearing aid OR TX osseointegrated hearing aids OR CROS
AND
((TX Unilateral OR TX one-sided OR TX single-sided) AND (TX deaf OR deafness OR TX hearing impairment)) OR TX hearing loss, unilateral

30 results

PsycInfo (2011-02-10)
bone-anchored hearing aid.mp. OR bone-anchored hearing aids.mp. OR BAHA.mp. OR osseointegrated hearing aids.mp. OR osseointegrated aids.mp. OR CROS.mp. OR Contralateral Routing of Signals.mp.

AND

((unilateral.mp. OR one-sided.mp. OR single-sided.mp.) AND (exp deaf OR deafness.mp.

OR hearing impairment)) OR hearing loss, unilateral.mp.

4 results

CRD (2011-02-10)
BAHA OR (bone-anchored AND hearing AND aid) OR (bone-anchored AND hearing AND Aids) OR CROS

13 results

CADTH (Canadian Agency for Drugs and Technologies in Health) (2011-02-10)

1 results

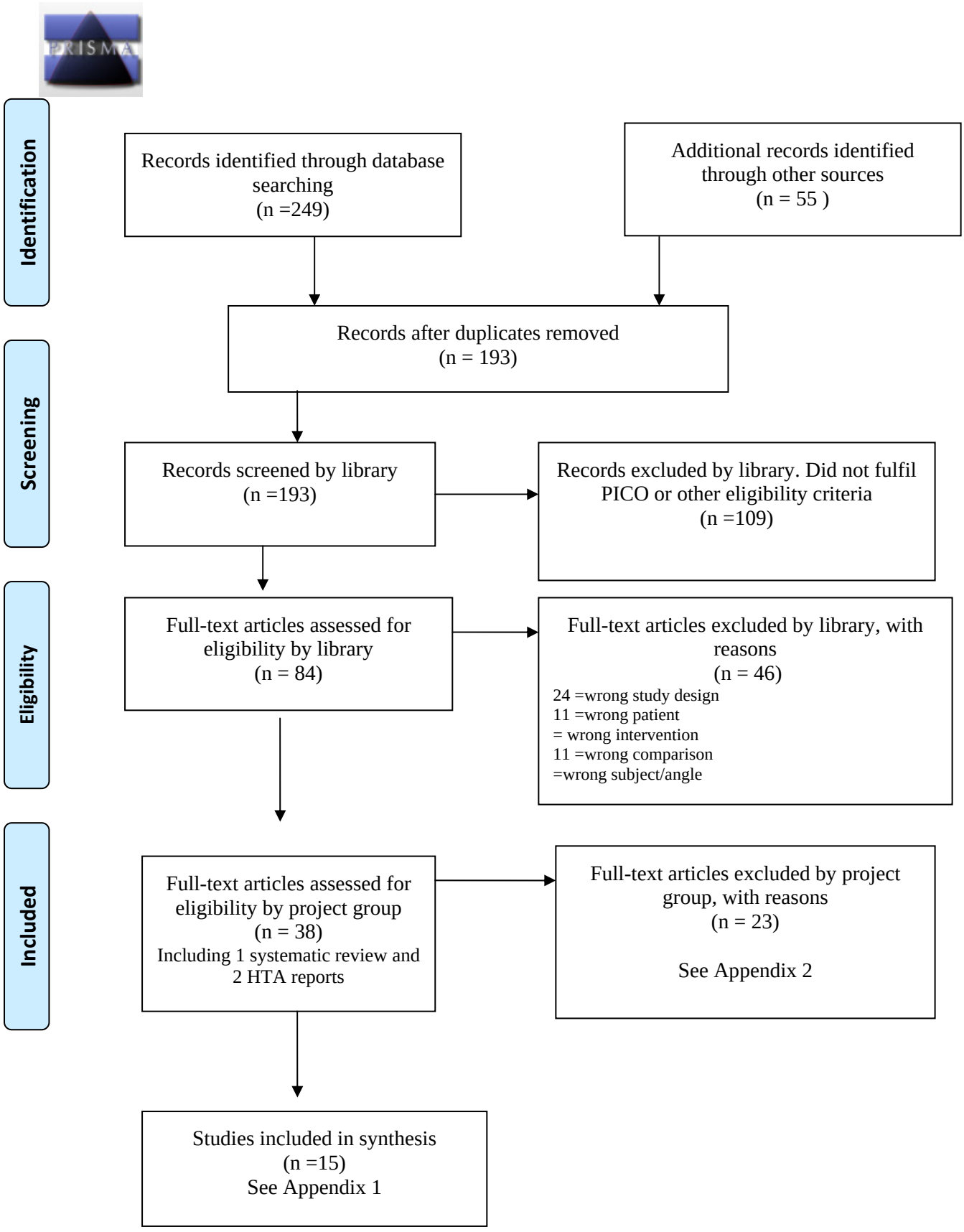
SBU, Kunnskapssenteret, Sundhedsstyrelsen
Nothing new was identified.

Reference lists:
A comprehensive review of reference lists brought no new references.

Exklusions- och inklusionskriterier
Studietyp:
- Studies with some kind of control group (RCT/Observation studies)
- Case series ≥ 30 patients – only complications
- Systematic reviews
- No case reports or review articles

Limits
Language: English, Danish, Norwegian, Swedish and non English with English abstracts
Publication date from 1977-

Selection process – flow diagram



References

Included articles:

Bosman AJ, Hol MK, Snik AF, Mylanus EA, Cremers CW. Bone-anchored hearing aids in unilateral inner ear deafness. Acta Otolaryngol. 2003 Jan; 123(2):258-60.

de Wolf MJ, Hol MK, Huygen PL, Mylanus EA, Cremers CW. Clinical outcome of the simplified surgical technique for BAHA implantation. Otol Neurotol. 2008 Dec; 29 (8):1100-8.

Hol MKS, Kunst SJW, Snik AFM, Cremers CWRJ. Pilot study on the effectiveness of the conventional CROS, the transcranial CROS and the BAHA transcranial CROS in adults with unilateral inner ear deafness. European Archives of Oto-Rhino-Laryngology. 2010b June; 267 (6):889-96.

Hol MKS, Kunst SJW, Snik AFM, Bosman AJ, Mylanus EAM, Cremers CWR. Bone-anchored hearing aids in patients with acquired and congenital unilateral inner ear deafness (Baha CROS): clinical evaluation of 56 cases. Annals of Otology, Rhinology & Laryngology. 2010a: 119(7):447-54.

House JW, Kutz Jr JW, Chung J, Fisher LM. Bone-anchored hearing aid subjective benefit for unilateral deafness. Laryngoscope. 2010 March; 120 (3):601-7.

House JW, Kutz JW, Jr. Bone-anchored hearing aids: incidence and management of postoperative complications. Otol Neurotol. 2007 Feb; 28(2):213-7.

Mace ATM, Isa A, Cooke LD. Patient quality of life with bone-anchored hearing aid: 10-year experience in Glasgow, Scotland. Journal of Laryngology and Otology. 2009 Sept; 123 (9):964-8.

McDermott AL, Williams J, Kuo M, Reid A, Proops D. The birmingham pediatric bone-anchored hearing aid program: a 15-year experience. Otol Neurotol. 2009 Feb; 30 (2): 178-83.

Martin TP, Lowther R, Cooper H, Holder RL, Irving RM, Reid AP, et al. The bone-anchored hearing aid in the rehabilitation of single-sided deafness: experience with 58 patients. Clin Otolaryngol. 2010 Aug; 35(4):284-90.

Reyes RA, Tjellström A, Granström G. Evaluation of implant losses and skin reactions around extraoral bone-anchored implants: A 0- to 8-year follow-up. Otolaryngol Head Neck Surg. 2000 Feb; 122 (2): 272-6.

Shirazi MA, Marzo SJ, Leonetti JP. Perioperative complications with the bone-anchored hearing aid. Otolaryngol Head Neck Surg. 2006 Feb; 134(2):236-9.

Van de Berg R, Stokroos RJ, Hof JR, Chenault MN. Bone-anchored hearing aid: a comparison of surgical techniques. Otol Neurotol. 2010 Jan; 31 (1): 129-35.

Van Rompaey V, Claes G, Verstraeten N, van Dinther J, Zarowski A, Offeciers E, et al. Skin reactions following BAHA surgery using the skin flap dermatome technique. Eur Arch Otorhinolaryngol.2011 Oct; 268:373-76.

Wazen JJ, Young DL, Farrugia MC, Chandrasekhar SS, Ghossaini SN, Borik J, et al. Successes and complications of the Baha system. Otol Neurotol. 2008 Dec; 29(8):1115-9.

Welling DB, Glasscock ME, 3rd, Woods CI, Sheffey RC. Unilateral sensorineural hearing loss rehabilitation. Otolaryngol Head Neck Surg. 1991 Dec; 105(6):771-6.

Excluded articles:

Andersen HT, Schroder SA, Bonding P. Unilateral deafness after acoustic neuroma surgery: subjective hearing handicap and the effect of the bone-anchored hearing aid. Otol Neurotol. 2006 Sep; 27(6):809-14.

Arndt S, Aschendorff A, Laszig R, Beck R, Schild C, Kroeger S, et al. Comparison of pseudobinaural hearing to real binaural hearing rehabilitation after cochlear implantation in patients with unilateral deafness and tinnitus. Otol Neurotol. 2010 Jan; 32(1):39-47.

Bergeron FF. Bone-anchored hearing aids: summary: report prepared for AETMIS. Québeck May 2006

Bone anchored hearing aid: an evidence-based analysis. Ontario Health Technology Assessment series 2002; Vol. 2, No 3. 47 s.

Bovo R, Prosser S, Ortoro RP, Martini A. Speech recognition with BAHA simulator in subjects with acquired unilateral sensorineural hearing loss. Acta Oto-Laryngologica, 2011: Early Online, 1-7.

Christensen L, Richter GT, Dornhoffer JL. Update on bone-anchored hearing aids in pediatric patients with profound unilateral sensorineural hearing loss. Arch Otolaryngol Head Neck Surg. 2010 Feb; 136(2):175-7.

CADTH. Completely-in-the Canal and Bone Anchored Hearing Aids: A review of the Clinical Effectiveness and Cost-effectiveness, 2010.

Danhauer JL, Johnson CE, Mixon M. Does the evidence support use of the Baha implant system (Baha) in patients with congenital unilateral aural atresia? J Am Acad Audiol. Apr; 21(4):274-86.

Gluth MB, Eager KM, Eikelboom RH, Atlas MD. Long-term benefit perception, complications, and device malfunction rate of bone-anchored hearing aid implantation for profound unilateral sensorineural hearing loss. Otol Neurotol. 2010 Dec; 31(9):1427-34.

Hol MKS, Bosman A, Snik AFM, Mylanus, Cremers CWR. Bone-anchored hearing aid in unilateral ear deafness: a study of 20 patients. Audiol Neurootol; 2004 Sept-Oct; 9(5): 274-81

Hol MKS, Bosman A, Snik AFM, Mylanus, Cremers CWR. Bone-anchored hearing aids in unilateral inner ear deafness: an evaluation of audimetric and patient outcome measurements. Otology & Neurotology 2005a Sept; 26(5): 999-106.

Hol MKS, Bosman A, Snik AFM, Mylanus, Cremers CWR. Does the bone-anchored hearing aid have a complementary effect on audiological and subjective outcomes in patients with unilateral conductive hearing loss? Audiol Neurootol 2005b May-Jun; 10(3): 159-68.

Kunst SJW, Leijendeckers JM, Mylanus EAM, Hol MKS, Snik AFM, Cremers CWRJ. Bone-anchored hearing aid system application for unilateral congenital conductive hearing impairment: Audiometric results. Otology and Neurotology. 2008 Jan ; 29 (1):2-7.

Lin LM, Bowditch S, Anderson MJ, May B, Cox KM, Niparko JK. Amplification in the rehabilitation of unilateral deafness: speech in noise and directional hearing effects with bone-anchored hearing and contralateral routing of signal amplification. Otol Neurotol. 2006 Feb; 27(2):172-82.

Linstrom CJ, Silverman CA, Yu GP. Efficacy of the bone-anchored hearing aid for single-sided deafness. Laryngoscope. 2009 Apr; 119(4):713-20.

McLarnon CM, Davison T, Johnson IJM. Bone-Anchored Hearing Aid: Comparison of Benefit by Patient Subgroups. Laryngoscope. 2004 May; 114 (5):942-4.

Niparko JK, Cox KM, Lustig LR. Comparison of the bone anchored hearing aid implantable hearing device with contralateral routing of offside signal amplification in the rehabilitation of unilateral deafness. Otol Neurotol. 2003 Jan;24(1):73-8.

Pfiffner F, Kompis M, Stieger C. Bone-anchored Hearing Aids: correlation between pure-tone thresholds and outcome in three user groups. Otol Neurotol. 2009 Oct; 30(7):884-90.

Priwin C, Jonsson R, Hultcrantz M, Granstrom G. BAHA in children and adolescents with unilateral or bilateral conductive hearing loss: a study of outcome. Int J Pediatr Otorhinolaryngol. 2007 Jan; 71(1):135-45.

Vaneecloo FM, Ruzza I, Hanson JN, Gerard T, Dehaussy J, Cory M, et al. [The monaural pseudo-stereophonic hearing aid (BAHA) in unilateral total deafness: a study of 29 patients]. Rev Laryngol Otol Rhinol (Bord). 2001; 122(5):343-50.

Wazen JJ, Spitzer JB, Ghossaini SN, Fayad JN, Niparko JK, Cox K, et al. Transcranial contralateral cochlear stimulation in unilateral deafness. Otolaryngol Head Neck Surg. 2003 Sep; 129(3):248-54.

Wazen JJ, Van Ess MJ, Alameda J, Ortega C, Modisett M, Pinsky k. The Baha system in patients with single-sided deafness and contralateral hearing loss. Otolaryngol Head Neck Surg 2010 Apr; 142(4): 554-559.

Yuen HW, Bodmer D, Smilsky K, Nedzelski JM, Chen JM. Management of single-sided deafness with the bone-anchored hearing aid. Otolaryngol Head Neck Surg. 2009 Jul; 141(1):16-23.

Other:

Andersson E, Andersson M, Börjesson E, Heneskog R, Jönsson R, Lundqvist AL et al. Spädbarn med hörselnedsättning: diagnostik och habilitering. Vällingby: Hjälpmedelsinstitutet; Göteborg:- Västra Götalandsregionen, 2002 [updated 2010 Feb 1; cited 2011 Sept 21]. Available from: http://www.hi.se/Global/pdf/2002/02364.pdf

Borton SA, Mauze E, Lieu JE. Quality of life in children with unilateral hearing loss: a pilot study. Am J Audiol. 2010 Jun;19(1):61-72.

[Checklists from SBU regarding randomized controlled trials. [Internet]. [cited 2011 Oct 13] Available from:http://www.sahlgrenska.se/upload/SU/HTA-centrum/Hj%c3%a4lpmedel%20under%20projektet/SBU_granskningsmall_RCT.pdf

Gatehouse S, Noble W. The Speech, Spatial and Qualities of Hearing Scale (SSQ). Int J Audiol. 2004 Feb;43(2):85-99.

GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19; 328(7454):1490-4.

GRADE Working Group. List of GRADE working group publications and grants [Internet]. [Place unknown]: GRADE Working Group, c2005-2009 [cited 2011 Oct 13]. Available from: http://www.gradeworkinggroup.org/publications/index.html

Harford E, Barry J. A rehabilitative approach to the problem of unilateral hearing impairment: the contralateral routing of signals CROS. J Speech Hear Disord. 1965 May; 30:121-38.

Holmgren S, Bertilsson Uleberg G, editors. RED10 research evaluation : reports from the evaluation of all research at the University of Gothenburg 2010. Göteborg: University of Gothenburg, 2011

Lieu JE, Tye-Murray N, Karzon RK, Piccirillo JF. Unilateral hearing loss is associated with worse speech-language scores in children. Pediatrics. 2010 Jun;125(6):e1348-55.

Lieu JE. Speech-language and educational consequences of unilateral hearing loss in children. Arch Otolaryngol Head Neck Surg. 2004 May;130(5):524-30.

Martinez-Cruz CF, Poblano A, Conde-Reyes MP. Cognitive performance of school children with unilateral sensorineural hearing loss. Arch Med Res. 2009 Jul;40(5):374-9.

Mehl AL, Thomson V. The Colorado newborn hearing screening project, 1992-1999: on the threshold of effective population-based universal newborn hearing screening. Pediatrics. 2002 Jan; 109 (1): E7.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21; 6(7):e1000097.

Monksfield P, Jowett S, Reid A, Proops D. Cost-effectiveness Analysis of the Bone-Anchored Hearing Device. Otol Neurotol. 2011 Oct; 32 (8): 1192-7.

[Nyren, Olle. Karolinska institutet. Checklists original articles not RCT]. [Internet]. [cited 2011 Oct 13] Available from: http://www.sahlgrenska.se/upload/SU/HTA-centrum/Hj%c3%a4lpmedel%20under%20projektet/SBU%20granskningsmall%20utan%20RCT%20o%20SR%202011.pdf

Schrøder SA, Ravn T, Bonding P. BAHA in single-sided deafness: patient compliance and subjective benefit. Otol Neurotol. 2010 Apr; 31(3):404-8.

Vartiainen E, Karjalainen S. Prevalence and etiology of unilateral sensorineural hearing impairment in a Finnish childhood population. Int J Pediatr Otorhinolaryngol. 1998 May 15; 43 (3): 253-9.

Summary of Findings Table
Bone anchored hearing aid (BAHA) in comparison to contralateral routing of signals (CROS) or no intervetion

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Level of evidence GRADE
Speech recognition								
3	1 RCT 2 observational studies	Very serious limitations (-2)	No important inconsistency	Uncertainty (-1)	Imprecision (-1)	Unlikely	Not relevant	⊕ Very low
Sound localisation								
3	1 RCT 2 observational studies	Very serious limitations (-2)	No important inconsistency	Uncertainty (-1)	Imprecision (-1)	Unlikely	Not relevant	⊕ Very low
Subjective experience								
4	1 RCT 3 observational studies	Very serious limitations (-2)	Some inconsistency (?)	Uncertainty (-1)	Imprecision (-1)	Unlikely	Not relevant	⊕ Very low

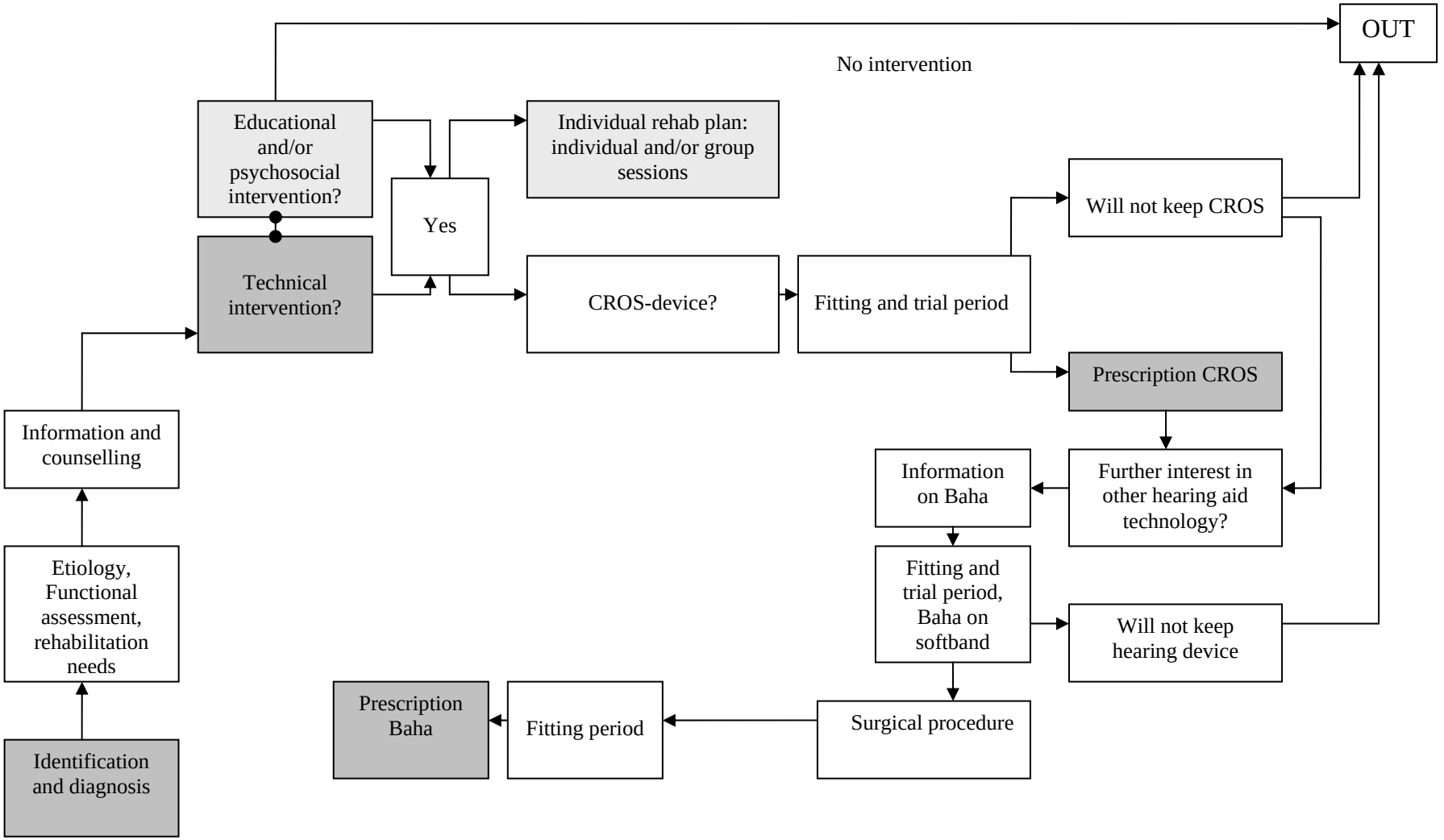
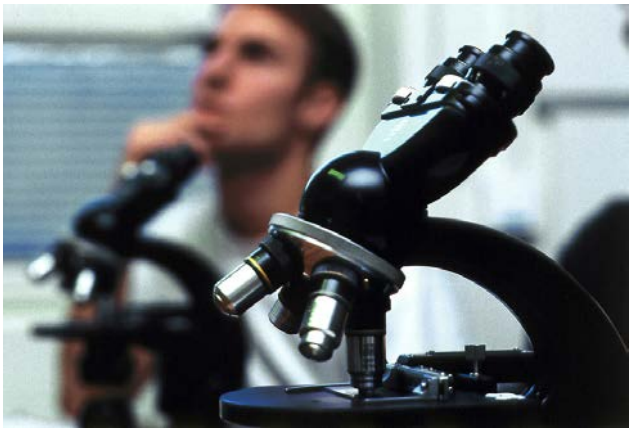


Figure 1. The normal pathway of a patient with unilateral severe hearing loss through the health care system. After prescription of hearing device, the patient will return for service, reparation of the hearing aid, and re-fitting after 5-7 years.



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

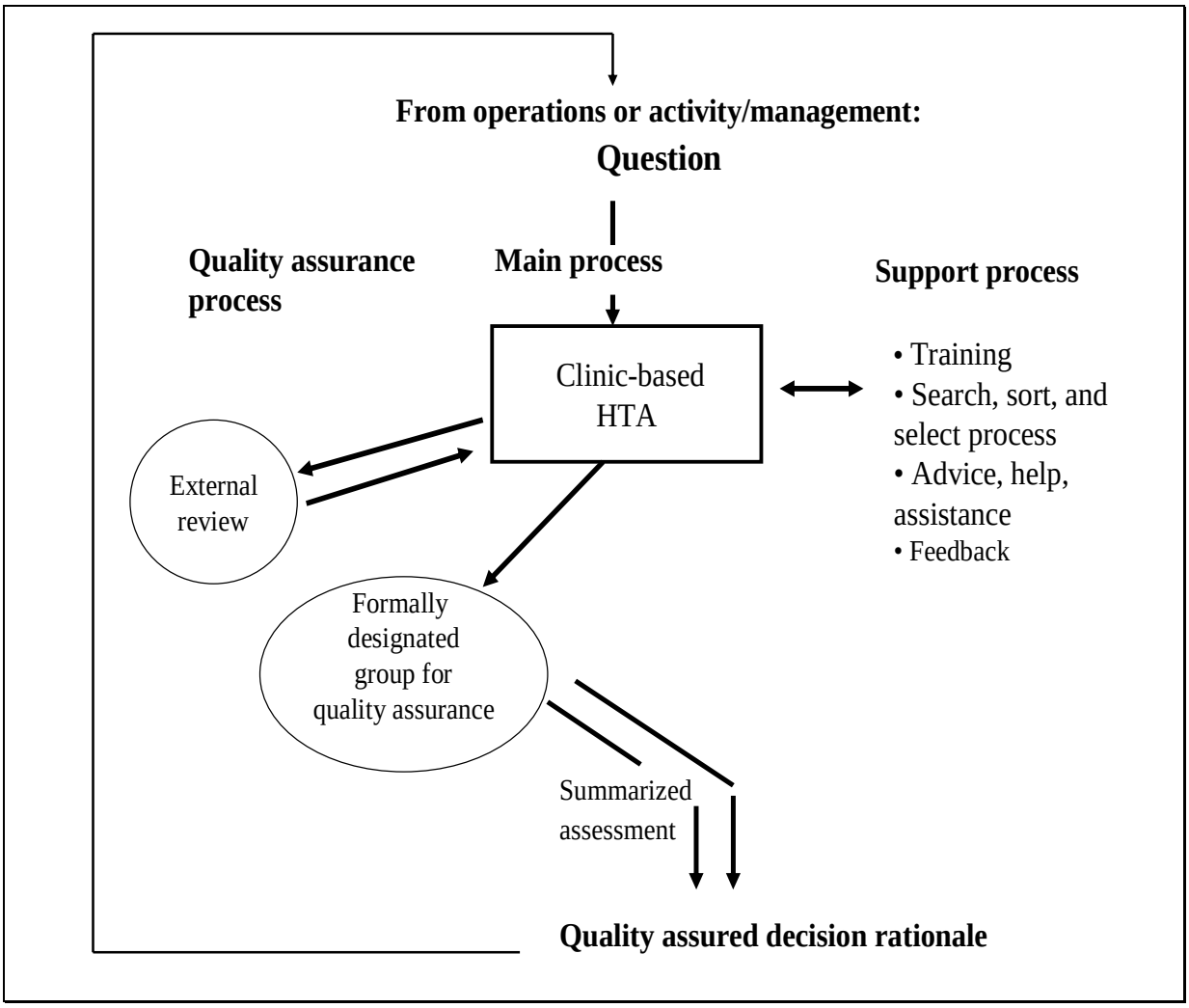
High quality of evidence	= ⊕⊕⊕⊕
Moderate quality of evidence	= ⊕⊕⊕
Low quality of evidence	= ⊕⊕
Very low quality of evidence	= ⊕

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

For diagnostic studies, the GRADE system should be applied for clinical outcomes and we have thus chosen not to use it for diagnostic accuracy studies.. In the present report, we have evaluated the level of evidence for diagnostic accuracy according to the system previously used by SBU, (Swedish Council on Health Technology Assessment), briefly described below.

High level of evidence
At least two studies of high quality or a systematic review of good quality
Moderate level of evidence
One study of high quality and at least two studies of moderate quality
Low level of evidence
At least two studies of moderate quality
Very low level of evidence
Only studies of low quality

Christina Bergh, Professor, MD.
Head of HTA-centre


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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Clinical Policy Bulletin:
Bone-Anchored Hearing Aid
Number: 0403

Policy History
- Last Review: 02/07/2014
- Effective: 03/09/2000
- Next Review: 04/24/2014
- Review History
- Definitions

Additional Information
- Clinical Policy Bulletin Notes

Policy

1. Aetna considers implantable bone-anchored hearing aids (BAHAs) or temporal bone stimulators medically necessary prosthetics for persons aged 5 years and older with a unilateral or bilateral conductive or mixed conductive and sensorineural hearing loss who have any of the following conditions, where the condition prevents restoration of hearing using a conventional air-conductive hearing aid and who meet the audiologic criteria below:

    1. Congenital or surgically induced malformations of the external ear canal or middle ear (such as aural atresia); *or*
    2. Dermatitis of the external ear, including hypersensitivity reactions to ear moulds used in air conduction hearing aids; *or*
    3. Hearing loss secondary to otosclerosis in persons who can not undergo stapedectomy; *or*
    4. Severe chronic external otitis or otitis media; *or*
    5. Tumors of the external ear canal and/or tympanic cavity; *or*
    6. Other conditions in which an air-conduction hearing aid is contraindicated.

    Audiologic criteria:

    1. Unilateral implant: Conductive or mixed (conductive and sensorineural) hearing loss with pure tone average bone conduction threshold (measured at 0.5, 1, 2, and 3 kHz) less than or equal to 45 dB HL (BAHA Divino, BAHA BP100), 55 dB HL (BAHA Intenso, Cochlear Baha 3 Power [BP110]) or 65 dB HL (BAHA Cordelle II).
    2. Bilateral implant: Moderate-to-severe bilateral symmetric conductive or mixed (conductive and sensorineural) hearing loss, meeting above-listed bone conduction thresholds in both ears. Symmetric bone conduction threshold is defined as less than:

        1. 10 dB average (measured at 0.5, 1, 2 and 4 kHz) or less than 15 dB at individual frequencies (BAHA Divino, BAHA BP100); *or*
        2. 10 dB average difference between ears (measured at 0.5, 1, 2, and 3 kHz), or less than a 15 dB difference at individual frequencies (BAHA Cordelle II, BAHA Intenso).

2. Aetna considers an implantable BAHA for conductive or mixed hearing loss experimental and investigational when criteria are not met because of insufficient evidence in the peer-reviewed published medical literature.

3. Aetna considers the use of an implantable BAHA medically necessary in persons with unilateral sensorineural hearing loss (single-sided deafness, i.e., deafness in one ear while the other ear has normal hearing). Aetna considers the use of an implantable BAHA experimental and investigational for bilateral pure sensorineural hearing loss, and for all other indications becuase its effectiveness for indications other than the ones listed above has not been established.

4. Aetna considers intra-oral bone conduction hearing aids (e.g., the SoundBite hearing system) for the treatment of hearing loss experimental and investigational becuase their effectiveness have not been established.

5. Aetna considers partially implantable bone conduction hearing systems using magnetic coupling for acoustic transmission (e.g., the Otomag Alpha 1(M) bone conduction hearing system) for the treatment of hearing loss experimental and investigational becuase their effectiveness have not been established.

Note: Aetna follows Medicare rules in considering osseointegrated implants, such as implantable BAHAs and temporal bone stimulators, as prosthetics. Medicare considers as prosthetics "osseointegrated implants, i.e., devices implanted in the skull that replace the function of the middle ear and provide mechanical energy to the cochlea via a mechanical transducer." Non-osseointegrated hearing devices (e.g., BAHA Soft Band, SoundBite) are not covered under plans that exclude coverage of hearing aids. Please check benefit plan descriptions.

See also CPB 0013 - Cochlear Implants and Auditory Brainstem Implants; and CPB 0612 - Implantable Hearing Aids.

Background

The bone-anchored hearing aid (BAHA) is a bone-conduction hearing aid that allows direct bone-conduction through a titanium implant and has become available as an acceptable alternative if an air-conduction hearing aid is contraindicated. The BAHA transmits sound vibrations through the skull bone via a skin-penetrating titanium implant, and then are further transmitted to the cochlea, bypassing the middle ear. Several clinical trials have shown its efficacy in patients with a conductive or mixed hearing loss. Indications for the BAHA include hearing loss from congenital ear problems, chronic suppurative otitis media, and in some cases otosclerosis as a third treatment option in those who can not or will not undergo stapedectomy. A second group of potential candidates are patients who suffer from an almost instantaneous skin reaction to any kind of ear mold. In some patients, the benefits are not necessarily those in hearing ability but relate to cosmetic or comfort improvements. Pre-operative assessment of the size of the air-bone gap is of some help to predict whether speech recognition may improve or deteriorate with the BAHA compared with the air-conduction hearing aid.

There is evidence in the peer-reviewed published medical literature to support the use of BAHAs over air conduction hearing aids, however, most of the studies have focused on individuals who suffer from single sided deafness, with unilateral sensorineural deafness in one ear while the other ear has normal hearing. The Food and Drug Administration

(FDA) has cleared for marketing the bone anchored hearing aid for individuals aged 5 years and older who have conductive or mixed hearing loss and for patients with sensorineural deafness in one ear and normal hearing in the other based on a 510(k) application. Such clearance was granted based on a determination that the BAHA was substantially equivalent to a contralateral routing of sound (CROS) air conduction hearing aid. A unilateral implant is used for individuals with unilateral conductive or mixed hearing loss and for unilateral sensorineural hearing loss. According to the FDA-approved indications, a bilateral implant is intended for patients with bilaterally symmetric moderate to severe conductive or mixed hearing loss.

In a recently published meta-analysis of the evidence for BAHA for single-sided deafness, Baguley and colleagues (2006) explained that acquired unilateral sensorineural hearing loss reduces the ability to localize sounds and to discriminate in background noise. Four controlled trials have been conducted to determine the benefit of contralateral BAHAs over CROS hearing aids and over the unaided condition. Speech discrimination in noise and subjective questionnaire measures of auditory abilities showed an advantage for BAHA over CROS and over unaided conditions. However, these studies did not find significant improvements in auditory localization with either aid. The investigators noted that these conclusions should be interpreted with caution because these studies have material shortfalls: (i) the BAHA was always trialled after the CROS aid; (ii) CROS aids were only trialled for 4 weeks; (iii) none used any measure of hearing handicap when selecting subjects; (iv) 2 studies have a bias in terms of patient selection; (v) all studies were under-powered; and (vi) double reporting of patients occurred (Baugley et al, 2006).

Priwin et al (2007) investigated (i) whether bilateral BAHAs in children with conductive bilateral hearing loss provided additional hearing benefits, (ii) the effects of unilateral hearing aids in children with conductive unilateral hearing loss, and (iii) the auditory problems of children with conductive unilateral or bilateral hearing loss. This prospective case series included 22 children with either conductive unilateral hearing loss (unaided or with unilateral hearing aid) or conductive bilateral hearing loss (with unilateral or bilateral BAHAs) and 15 controls. The investigators tested baseline audiometry, tone thresholds in a sound field, and speech recognition in noise and sound localization with and without unilateral and bilateral hearing aids. Two self-assessment questionnaires were completed. The investigators reported 2 problem areas in the children with hearing impairment: (i) reactions to sounds, and (ii) intelligibility of speech. An additional BAHA in the children with bilateral hearing loss resulted in a tendency to have improved hearing in terms of better sound localization and speech recognition in noise. Fitting of unilateral hearing aids in the children with unilateral hearing loss gave some supplementary benefit in terms of better speech recognition in noise but no positive effect on ability to localize sound could be detected. Even so, all children fitted with hearing aids, either unilaterally or bilaterally, reported a positive outcome with their devices in the self-assessment questionnaire. The investigators concluded that the fitting of bilateral BAHAs in children with bilateral hearing loss and of a single-sided hearing aid in children with unilateral hearing loss appears to have some supplementary audiological benefits and also renders high patient satisfaction.

When suggested indications for treatment with the BAHA system are followed, the success rate is very high. The improved quality of life reported by the patients is a combination of improved quality of sound (warble tone threshold, speech reception threshold, and discrimination in noise), improved comfort, and relief from middle ear and ear canal disease occasioned by conventional hearing aids.

An assessment of the BAHA device by the Institute for Clinical Effectiveness and Health Policy (Pichon-Rivere et al, 2009) concluded that there is evidence that BAHA is useful for people with conductive-type hearing loss who can not undergo surgery or who have

contraindications or adverse effects to hearing aids. If implantation is used, it should be implanted to patients over 5 years old and by specially trained staff in an operating room. Evidence comes, however, from observational studies, many of which include a few participants.

Although no longer marketed, the Audiant (Medtronic Xomed, Inc., Jacksonville, FL) Bone Conductor, also known as the temporal bone stimulator, is an FDA-approved implanted device with an external processor that uses transcutaneous inductive electromagnetic energy to cause vibration of an implanted titanium magnet screwed into the temporal bone. Like the currently marketed BAHA device, the Audiant Bone Conductor is also based on a bone conduction concept, and is also indicated for persons with conductive or mixed conductive and sensorineural hearing loss who have conditions that prevent restoration of hearing using a conventional air-conductive hearing aid.

Hol et al (2010) evaluated the effectiveness of 3 CROS hearing aids in adults (n = 10 with unilateral inner ear deafness and normal hearing in the contralateral ear: (i) the CROS hearing aid, (ii) the completely in the canal hearing aid, and (iii) the BAHA CROS (BAHA). Each of the 3 hearing aids was tried in a random order for a period of 8 weeks. Audiometric performance, including speech-in-noise, directional hearing and subjective benefit were measured after each trial period, using the Abbreviated Profile of Hearing Aid Benefit (APHAB), SSQ and single-sided deafness questionnaire. Sound localization performance was essentially at chance level in all 4 conditions. Mixed results were seen on the other patient outcome measures that alternated in favor of one of the 3 CROS devices. After the trial, 3 patients chose to be fitted with the BAHA CROS and 1 with the conventional CROS. The authors concluded that most of the patients experienced some degree of benefit with each of the 3 hearing aids. Preference for one of the 3 hearing aids was independent of the order in which they were tried. It would be worthwhile to formulate selection criteria; still, the authors recommended that all patients with unilateral inner ear deafness should be offered a trial with at least the BAHA CROS.

de Wolf and colleagues (2011a) stated that a study performed in the 1990s with analog linear hearing aids showed that in patients with mixed hearing loss and an air-bone gap that exceeded 25 to 30 dB, speech perception was better with a BAHA than with a conventional behind-the-ear (BTE) device. The objective of the present study was to examine if this conclusion applies to today's digital BTEs with feedback cancellation and whether the cross-over point still occurs at an air-bone gap of 25 to 30 dB. Experienced unilateral BAHA users with the latest digital Baha processors were fitted with a powerful BTE with feedback cancellation. After an acclimatization period of 4 weeks, aided thresholds and speech recognition scores were determined and compared to those recorded previously with the BAHA. To obtain patients' opinions, a disability-specific questionnaire was used. Participants comprised 16 subjects with bilateral mixed hearing loss. Audiometric and speech recognition data showed similar trends to those described previously, but the cross-over point had shifted to an air-bone gap of 30 to 35 dB. In the questionnaire, the BTE was rated higher than the BaHA, except by the patients with an air-bone gap that exceeded an average of 45 dB. The authors concluded that in patients with mixed hearing loss whose air-bone gap exceeded 35 dB, speech recognition is likely to be better with a BAHA than with a BTE. Thus, the BAHA should receive greater consideration when mixed hearing loss is combined with a significant air-bone gap, even when there are no contraindications for BTEs.

de Wolf and colleagues (2011b) evaluated the benefits of a BAHA in the daily lives of hearing-impaired children. A total of 38 BAHA users with a minimum age of 4 years at BAHA fitting and 1 to 4 years of use were divided into groups with bilateral conductive or mixed hearing loss and either normal cognition or mental disability and a group with

unilateral conductive hearing loss. Main outcome measures included scores on the Glasgow Children's Benefit Inventory, APHAB, and Health Utilities Index Mark 3. The Glasgow Children's Benefit Inventory showed a subjective overall benefit of +32, +16, and +26 in the 3 groups (on a scale of -100 to +100). The APHAB also showed an overall mean benefit in the groups. On an individual level, a clinically significant benefit was reported by more children in the group with bilateral hearing loss and normal cognition (7 patients [70 %]) than in the unilateral hearing loss group (4 patients [27 %]). Overall mean health utility scores and disability index scores on the Health Utility Index Mark 3 were comparable among the 3 groups. The authors concluded that overall, BAHA fitting can be considered effective and beneficial in children with bilateral or unilateral hearing loss.

The SoundBite hearing system (Sonitus Medical, San Mateo, CA) allows people with single-sided deafness (SSD) to wear an intra-oral device and a small microphone in the deaf ear to regain lost hearing. A piezoelectric activator in a small removable unilateral oral appliance conducts sound through the bone via the teeth to the good ear. Currently, there is insufficient evidence to support the use of an intra-oral bone conduction hearing aid for the treatment of hearing loss. The quality of the studies was low due to small study populations, short follow-up, and the lack of randomization and appropriate control groups. Future studies with larger populations of patients wearing the device for longer periods are needed to evaluate hearing benefits and device safety.

Popelka et al (2010) stated that a new approach for SSD has been proposed that optimizes microphone location and delivers sound by bone conduction through a removable oral appliance. Measures in the laboratory using normal-hearing subjects indicated that the device provides useful gain and output for SSD patients, is comfortable, does not seem to have detrimental effects on oral function or oral health, and has several advantages over existing devices. Specifically, microphone placement is optimized for reducing the auditory deficit caused by SSD, frequency bandwidth is much greater, and the system does not require surgical placement. Auditory performance in a small sample of SSD subjects indicated a substantial advantage compared with not wearing the device. The authors noted that future studies will involve performance measures on SSD patients wearing the device for longer periods.

Murray et al (2011a) determine the benefit, safety and effectiveness, of a new intra-oral conduction device (SoundBite Hearing System) for SSD. Adults (aged between greater than 18 and less than 80 years) with acquired, permanent SSD (n = 28) and no current use of any SSD device were included in this study. Intervention was continual daily wear of the new device over a 30-day trial period. Main outcome measures included the Hearing in Noise Test (HINT), the Abbreviated Profile of Hearing Aid Benefit (APHAB), comprehensive pre-trial and post-trial medical, audiologic, and dental examinations and an SSD questionnaire. The Hearing in Noise Test scores improved an average of -2.5 dB after 30 days, compared with wearing no device ($p < 0.001$). The Abbreviated Profile of Hearing Aid Benefit scores improved ($p < 0.05$) for all subjects for the Global and Background Noise subscales and for all but 1 subject for the Reverberation and Ease of Communication subscales. There were no medical, audiologic, or dental complications. The authors concluded that the SoundBite system is safe and effective and provided substantial benefit for SSD patients with continual daily use over a 30-day period.

Murray et al (2011b) determined the long-term safety and benefit of the SoundBite Hearing System for SSD. Adults (n = 22) with acquired, permanent SSD and no current use of any other SSD device were included in this study. Main outcome measures included comprehensive medical, audiologic, and dental measures; aided thresholds; Abbreviated Profile of Hearing Aid Benefit scores, and an SSD questionnaire. There

were no related adverse events or changes in the medical or audiologic findings at the end of the trial compared with the beginning. There were no significant changes in the mean aided thresholds ($p > 0.01$) or the mean dental measures ($p > 0.05$) at 3 or 6 months compared with pre-trial measures. The mean Abbreviated Profile of Hearing Aid Benefit scores showed improvement ($p < 0.01$) for the Background Noise, Reverberation, and Ease of Communication subscales and the Global scale at 3 and 6 months. The results of the SSD questionnaire indicated that the vast majority (greater than 90 %) of the subjects reported satisfaction and improvement in a variety of areas after wearing the device long-term. The authors concluded that the SoundBite system is safe and continues to provide substantial benefit for SSD patients with continual daily use over a 6-month period.

The Otomag bone conduction hearing system (Sophono, Inc., Boulder, CO) is a partially implantable bone conduction hearing aid without a percutaneous abutment. The Otomag sound processor is attached magnetically to an implanted magnet assembly. The magnetic field holds the sound processor against the head and vibration is transduced through direct contact with the patient's skin and the bone below. The principle of these bone conduction hearing aids is a magnetic coupling and acoustic transmission between implanted and external magnets. Currently, there is insufficient evidence that the Otomag bone conduction hearing system is beneficial for patients with hearing loss. Further investigation with larger populations and long-term follow-up are needed to evaluate improvement of hearing with this device.

Siegert (2011) developed new partially implantable bone conduction hearing aid without a percutaneous abutment and have been using them clinically for 4 years. The goal of this study was to evaluate clinical and audiological results. Magnets were implanted into shallow bone beds in a 1-step procedure. The skin area above the magnets was also reduced to a thickness of 4 to5 mm, which reduces the attenuation to less than 10 dB compared to direct bone stimulation. Over 100 patients have been implanted in the last 5 years. Except for temporary pressure marks in 4 %, which healed after careful shimming of the external base plate, there were no other complications. The author concluded that the holding strength of the external components is equivalent to partially implantable hearing aids and cochlea implants and the hearing improvement is similar to other bone conduction hearing aids. The author noted that the comfort and safety of this system is significantly improved compared to conventional or percutaneous bone conduction hearing aids. The main drawback of this study was the lack of a control group. These preliminary findings need to be validated by well-designed studies.

Kiringoda and Lustig (2013) summarized available peer-reviewed literature to describe the range and rate of complications related to osseo-integrated hearing aids in adult and pediatric patients. These investigators searched PubMed using the terms bone-anchored hearing aid for articles published in English between 2000 and 2011. They included all articles reporting complications rates, except those that were case reports, general review (not systematic review), or commentary, as well as those that did not include patient outcomes, that reported outcomes associated with non-standard implantation (e.g., 8.5-mm abutment) or were of poor study or reporting quality. After excluding articles that did not meet criteria, a total of 20 articles were identified, comprising 2,134 patients who underwent a total of 2,310 osseo-implants. Complications reported in the literature were typically minor in nature. Skin reactions from Holgers Grade 2 to 4 ranged from 2.4 % to 38.1 %. Failure of osseo-integration ranged from 0 % to 18 % in adult and mixed populations, and 0 % to 14.3 % in pediatric populations. The rate of revision surgery ranges from 1.7 % to 34.5 % in adult and mixed populations and 0.0 % to 44.4 % in pediatric patients, whereas the total rate of implant loss ranged from 1.6 % to 17.4 % in adult and mixed populations and from 0.0 % to 25 % in pediatric patients. The authors concluded that overall, the quality of large scale and/or prospective studies reporting the

incidence of complications after osseo-integrated hearing aid surgery is poor and lacks uniformity. However, based on available data, which shows a lack of major complications, osseo-integrated implantation is a safe procedure in both adult and pediatric populations. Moreover, they stated that well-designed, prospective studies with uniform reporting standards would allow greater comparison between techniques and more reliable analysis of complications of osseo-integration surgery of the temporal bone for cochlear stimulation.

Appendix

Table: Usual medically necessary frequency of replacement for BAHA parts

Replacement Parts	Life Expectancy
Batteries	72 per 6 months
Headband	1 per year
Processor	1 per 5 years

Adapted from: Wisconsin Department of Health and Family Services, 2005.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

69710

69711

69714

69715

69717

69718

Other CPT codes related to the CPB:

69550 - 69554

69660 - 69662

92521

92522

92523

92524

92551 - 92557, 92558, 92567 - 92569, 92579, 92582 - 92587

92626 - 92627

92630 - 92633

HCPCS codes covered if selection criteria is met:

L8690	Auditory osseointegrated device, includes all internal and external components
L8691	Auditory osseointegrated device, external sound processor, replacement
L8693	Auditory osseointegrated device abutment, any length, replacement only

Other HCPCS codes related to the CPB:

G0153	Services performed by a qualified speech-language pathologist in the home health or hospice setting, each 15 minutes
L8692	Auditory osseointegrated device, external sound processor, used without osseointegration, body worn, includes headband or other means of external attachment [excluded under plans that exclude coverage of hearing aids]
S9128	Speech therapy, in the home, per diem
V5008 - V5299	Hearing services

ICD-9 codes covered if selection criteria are met:

160.1	Malignant neoplasm of auditory tube, middle ear, and mastoid air cells
171.0	Malignant neoplasm of head, face and neck
173.2	Malignant neoplasm of skin of ear and external auditory canal
212.0	Benign neoplasm of nasal cavities, middle ear, and accessory sinuses
215.0	Benign neoplasm of head, face, and neck
216.2	Benign neoplasm of ear and external auditory canal
232.2	Carcinoma in situ of ear and external auditory canal
380.32	Acquired deformities of auricle or pinna [surgically induced malformations of external ear canal or middle ear]
381.10	Chronic serous otitis media, simple or unspecified [severe]
381.20	Chronic mucoid otitis media [severe]
381.3	Other and unspecified chronic nonsuppurative otitis media [severe]
382.2	Chronic atticoantral suppurative otitis media [severe]
382.3	Unspecified chronic suppurative otitis media [severe]
382.9	Unspecified otitis media [chronic severe]
387.0 - 387.9	Otosclerosis [causing hearing loss in persons who cannot undergo stapedectomy]
389.00 - 389.08	Conductive hearing loss
389.15	Sensorineural hearing loss, unilateral
389.20 - 389.22	Mixed conductive and sensorineural hearing loss
691.8	Other atopic dermatitis and related conditions
692.0 - 692.6,	Contact dermatitis and other eczema [external ear/hypersensitivity

692.81 692.83 - 692.9	reactions]
744.02	Other anomalies of external ear with impairment of hearing [congenital malformations of external ear canal]
744.03	Anomaly of middle ear, except ossicles [congenital malformations of middle ear]
744.04	Anomalies of ear ossicles [congenital malformations of middle ear]
744.3	Unspecified anomaly of ear [congenital malformations of external ear canal or middle ear]

ICD-9 codes not covered for indications listed in the CPB:

389.10 - 389.14, 389.16 - 389.18	Sensorineural hearing loss [other than unilateral]

SoundBite Hearing System [e.g., intra-oral bone conduction hearing aids] [excluded under plans that exclude coverage of hearing aids]:

No specific code

ICD-9 codes not covered for indications listed in the CPB:

389.00 - 389.9	Hearing loss

Otomag Alpha 1(M) Bone Conduction Hearing System [e.g., partially implantable bone conduction hearing systems]:

No specific code

ICD-9 codes not covered for indications listed in the CPB:

389.00 - 389.9	Hearing loss

The above policy is based on the following references:

1. Hakansson BE, Carlsson PU, Tjellstrom A, et al. The bone-anchored hearing aid: Principal design and audiometric results. Ear Nose Throat J. 1994;73(9):670-675.
2. Tjellstrom A, Hakansson B. The bone-anchored hearing aid. Design principles, indications, and long- term clinical results. Otolaryngol Clin North Am. 1995;28(1):53-72.
3. Snik AF, Mylanus EA, Cremers CW. Bone-anchored hearing aids in patients with sensorineural hearing loss and persistent otitis externa. Clin Otolaryngol. 1995;20(1):31-35.
4. Browning GG, Gatehouse S. Estimation of the benefit of bone-anchored hearing aids. Ann Otol Rhinol Laryngol. 1994;103(11):872-878.
5. Cooper HR, Burrell SP, Powell RH, et al. The Birmingham bone anchored hearing aid programme: Referrals, selection, rehabilitation, philosophy and adult results. J Laryngol Otol Suppl. 1996;21:13-20.
6. Niehaus HH, Helms J, Muller J. Are implantable hearing devices really necessary? Ear Nose Throat J. 1995;74(4):271-274, 276.
7. Powell RH, Burrell SP, Cooper HR, et al. The Birmingham bone anchored hearing aid programme: Paediatric experience and results. J Laryngol Otol Suppl. 1996;21:21-29.
8. Burrell SP, Cooper HC, Proops DW. The bone anchored hearing aid--the third option for otosclerosis. J Laryngol Otol Suppl. 1996;21:31-37.

9. Macnamara M, Phillips D, Proops DW. The bone anchored hearing aid (BAHA) in chronic suppurative otitis media (CSOM). J Laryngol Otol Suppl. 1996;21:38-40.
10. Granstrom G, Tjellstrom A. The bone-anchored hearing aid (BAHA) in children with auricular malformations. Ear Nose Throat J. 1997;76(4):238-240, 242, 244-247.
11. Mylanus EA, van der Pouw KC, Snik AF, et al. Intraindividual comparison of the bone-anchored hearing aid and air- conduction hearing aids. Arch Otolaryngol Head Neck Surg. 1998;124(3):271-276.
12. Wazen JJ, Caruso M, Tjellstrom A. Long-term results with the titanium bone-anchored hearing aid: The U.S. experience. Am J Otol. 1998;19(6):737-741.
13. Tjellstrom A, Hakansson B, Granstrom G. Bone-anchored hearing aids: Current status in adults and children. Otolaryngol Clin North Am. 2001;34(2):337-364.
14. Snik AF, Mylanus EA, Cremers CW. The bone-anchored hearing aid: A solution for previously unresolved otologic problems. Otolaryngol Clin North Am. 2001;34(2):365-372.
15. Shohet JA, Lee F. Implantable hearing devices. eMedicine ENT Topic 479. Omaha, NE: eMedicine.com; updated August 14, 2004. Available at: http://www.emedicine.com/ent/topic479.htm. Accessed July 19, 2005.
16. Cooper TJ, Tomlinson J, Sutton J, et al. The use of bone anchored hearing aids. Guidance Note for Purchasers. Sheffield, UK: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield; 1997.
17. UK National Health Service, Cambridgeshire and Peterborough Public Health Network. Bone anchored hearing aids (BAHAs). Policy. Cambridgeshire, UK: Cambridgeshire Health Authority Board; February 27, 2002.
18. Spitzer JB, Soha NG, Wazen JJ. Evolving applications in the use of bone-anchored hearing aids. Am J Audiology. 2002;11:96-103.
19. National Deaf Children's Society (NDCS). Quality standards in bone anchored hearing aids for children and young people. London, UK: NDCS; July 2003.
20. U.S. Food and Drug Administration (FDA). Branemark Bone Anchored Hearing Aid (BAHA). Summary of Safety and Effectiveness. 510(k) No. K021837. Rockville, MD: FDA; June 1, 2002.
21. Niparko JK, Cox KM, Lustig LR. Comparison of the bone anchored hearing aid implantable hearing device with contralateral routing of offside signal amplification in the rehabilitation of unilateral deafness. Otol Neurotol. 2003;24(1):73-78.
22. Wazem JJ, Spitzer JB, Ghossaini SN, et al. Transcranial contralateral cochlear stimulation in unilateral deafness. Otolaryngol Head Neck Surg. 2003;129:248-254.
23. Wazen JJ, Spitzer J, Ghossaini SN, et al. Results of the bone-anchored hearing aid in unilateral hearing loss. Laryngoscope. 2001;111(6):955-958.
24. Stenfelt S, Hakansson B, Jonsson R, Granstrom G. A bone-anchored hearing aid for patients with pure sensorineural hearing impairment: A pilot study. Scand Audiol. 2000;29(3):175-185.
25. McLarnon CM, Davison T, Johnson IJ. Bone-anchored hearing aid: Comparison of benefit by patient subgroups. Laryngoscope. 2004;114(5):942-944.
26. Ontario Ministry of Health and Long-Term Care, Medical Advisory Secretariat. Bone anchored hearing aid (BAHA). Health Technology Scientific Literature Review. Toronto, ON: Ontario Ministry of Health and Long-Term Care; September 2002. Available at: http://www.health.gov.on.ca/english/providers/program/. Accessed August 4, 2004.
27. Priwin C, Granstrom G. The bone-anchored hearing aid in children: A surgical and questionnaire follow-up study. Otolaryngol Head Neck Surg. 2005;132(4):559-565.
28. Hol MK, Snik AF, Mylanus EA, Cremers CW. Does the bone-anchored hearing aid have a complementary effect on audiological and subjective outcomes in patients with unilateral conductive hearing loss? Audiol Neurootol. 2005;10(3):159-168.
29. UK National Health Service (NHS), National Library for Health. Knowledge

update: Hearing aid provision and rehabilitation. Specialist Library for ENT and Audiology. London, UK: NHS; April 2006. Available at: www.library.nhs.uk/SpecialistLibraries/ Download.aspx?resID=124002. Accessed May 30, 2006.

30. Bergeron F. Bone-anchored hearing aid. AETMIS 06-05. Summary. Montreal, QC: Agence D'Evaluation des Technologies et des Modes D'Intervention en Santé (AETMIS); May 2006.
31. Parrella A, Mundy L. Bone anchored hearing aid (BAHA). Horizon Scanning Prioritising Summary - Volume 8. Adelaide, SA: Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (HealthPACT and MSAC); 2005.
32. Baguley DM, Bird J, Humphriss RL, Prevost AT. The evidence base for the application of contralateral bone anchored hearing aids in acquired unilateral sensorineural hearing loss in adults. Clin Otolaryngol. 2006;31(1):6-14.
33. Davids T, Gordon KA, Clutton D, Papsin BC. Bone-anchored hearing aids in infants and children younger than 5 years. Arch Otolaryngol Head Neck Surg. 2007;133(1):51-55.
34. Clark M, Mierzwinski-Urban M. Bone anchored hearing aid in adults. Health Technology Inquiry Service. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); September 28, 2007.
35. Wisconsin Department of Health and Family Services. Replacement parts for cochlear implant and bone-anchored hearing devices. Attachment 3. Wisconsin Medicaid and BadgerCare Update. No. 2005-20. Madison, WI: Wisconsin Department of Health and Family Services; March 2005. Available at: http://dhs.wisconsin.gov/medicaid/updates/2005/2005pdfs/2005-20.pdf. Accessed July 29, 2008.
36. U.S. Food and Drug Administration (FDA) 510(k). Branemark Bone Anchored Hearing Aid (BAHA) System. Summary of Safety and Effectiveness. 510(k) No. K984162. Rockville, MD: FDA; June 28, 1999. Available at: http://www.fda.gov/cdrh/pdf/k984162.pdf. Accessed on October 27, 2008.
37. U.S. Food and Drug Administration (FDA) 510(k). Bilateral fitting of BAHA. Summary of Safety and Effectiveness. 510(k) No. K011438. Rockville, MD: FDA; July 23, 2001. Available at: http://www.fda.gov/cdrh/pdf/k011438.pdf. Accessed on October 27, 2008.
38. U.S. Food and Drug Administration (FDA). BAHA Divino. Summary of Safety and Effectiveness. 510(k) No. K042017. Rockville, MD: FDA; August 26, 2004. Available at: http://www.fda.gov/cdrh/pdf4/k042017.pdf. Accessed on October 27, 2008.
39. U.S. Food and Drug Administration (FDA). BAHA Cordelle II. Summary of Safety and Effectiveness. 510(k) No. K080363. Rockville, MD: FDA; April 10, 2008. Available at: http://www.fda.gov/cdrh/pdf8/K080363.pdf. Accessed on October 27, 2008.
40. U.S. Food and Drug Administration (FDA). BAHA Intenso. Summary of Safety and Effectiveness. 510(k) No. K081606. Rockville, MD: FDA; August 28, 2008. Available at: http://www.fda.gov/cdrh/pdf8/K081606.pdf. Accessed on October 27, 2008.
41. U.S. Food and Drug Administration (FDA). BAHA BP100. Summary of Safety and Effectiveness. 510(k) No. K090720. Rockville, MD: FDA; June 17, 2009. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf9/K090720.pdf. Accessed June 17, 2010.
42. Priwin C, Jönsson R, Hultcrantz M, et al. BAHA in children and adolescents with unilateral or bilateral conductive hearing loss: A study of outcome. Int J Pediatr Otorhinolaryngol. 2007;71(1):135-145.
43. Centers for Medicare & Medicaid Services (CMS). Hearing aids and auditory

implants. Medicare Benefit Policy Manual, Ch. 16 - General Exclusions from Coverage, Sec. 100 (Rev. 39; Issued: 11-10-05; Effective: 11-10-05; Implementation: 12-12-05). Baltimore, MD: CMS; 2005. Available at: http://www.cms.hhs.gov/manuals/downloads/bp102c16.pdf. Accessed January 6, 2008.

44. Verhaegen VJ, Mulder JJ, Mylanus EA, et al. Profound mixed hearing loss: Bone-anchored hearing aid system or cochlear implant? Ann Otol Rhinol Laryngol. 2009;118(10):693-697.
45. Pichon-Riviere A, Augustovski F, Garcia Marti S, et al. BAHA devices in hypoacusia [summary]. IRR No. 171. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); 2009.
46. Christensen L, Richter GT, Dornhoffer JL. Update on bone-anchored hearing aids in pediatric patients with profound unilateral sensorineural hearing loss. Arch Otolaryngol Head Neck Surg. 2010;136(2):175-177.
47. Health Technology Inquiry Service (HTIS). Completely-in-the-canal and bone anchored hearing aids: A review of the clinical effectiveness and cost-effectiveness. Health Technology Assessment (HTA). Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); March 4, 2010.
48. Hol MK, Kunst SJ, Snik AF, Cremers CW. Pilot study on the effectiveness of the conventional CROS, the transcranial CROS and the BAHA transcranial CROS in adults with unilateral inner ear deafness. Eur Arch Otorhinolaryngol. 2010;267(6):889-896.
49. de Wolf MJ, Hendrix S, Cremers CW, Snik AF. Better performance with bone-anchored hearing aid than acoustic devices in patients with severe air-bone gap. Laryngoscope. 2011(a);121(3):613-616.
50. de Wolf MJ, Hol MK, Mylanus EA, et al. Benefit and quality of life after bone-anchored hearing aid fitting in children with unilateral or bilateral hearing impairment. Arch Otolaryngol Head Neck Surg. 2011(b);137(2):130-138.
51. Colquitt JL, Loveman E, Baguley DM, et al. Bone-anchored hearing aids for people with bilateral hearing impairment: A systematic review. Clin Otolaryngol. 2011;36(5):419-441.
52. Colquitt JL, Jones J, Harris P, et al. Bone-anchored hearing aids (BAHAs) for people who are bilaterally deaf: A systematic review and economic evaluation. Health Technol Assess. 2011;15(26):1-200, iii-iv.
53. Olsen SO, Glad H, Nielsen LH. Comparison of two bone anchored hearing instruments: BP100 and Ponto Pro. Int J Audiol. 2011;50(12):920-928.
54. Popelka G, Derebery J, Blevins N, et al. Preliminary evaluation of a novel bone-conduction device for single sided deafness. Otology and Neurology. 2010;31(3):492-497.
55. Popelka GR. SoundBite hearing system by Sonitus Medical: A new approach to single-sided deafness. Seminars in Hearing. 2010;31(4):393-409.
56. Miller RJ. It's time we listened to our teeth: The SoundBite hearing system. Am J Orthod Dentofacial Orthop. 2010;138(5):666-669.
57. Miller R, Hujoel P, Murray M, Popelka GR. Safety of an intra-oral hearing device utilizing a split-mouth research design. J Clin Dent. 2011;22(5):159-162.
58. Murray M, Popelk G, Miller R. Efficacy and safety of an in the mouth bone conduction device for single sided deafness. Otology and Neurology. 2011a;32(3):437-443.
59. Murray M, Miller R, Hujoel P, Popelka G. Long-term safety and benefit of a new intraoral device for single-sided deafness. Otology and Neurology. 2011b;32(8):1262-1269.
60. Siegert R. Partially implantable bone conduction hearing aids without a percutaneous abutment (Otomag): Technique and preliminary clinical results. Adv Otorhinolaryngol. 2011;71:41-46.

61. Kiringoda R, Lustig LR. A meta-analysis of the complications associated with osseointegrated hearing aids. Otol Neurotol. 2013;34(5):790-794.

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Medical Policy

Subject:	Bone-Anchored Hearing Aids		
Policy #:	SURG.00020	**Current Effective Date:**	10/08/2013
Status:	Reviewed	**Last Review Date:**	08/08/2013

Description/Scope

Conventional external hearing aids can be categorized as air conduction (AC) hearing aids or bone conduction (BC) hearing aids. An implantable bone conduction hearing aid, also called a bone-anchored hearing aid (BAHA®) (Cochlear Americas, Centennial, CO and Cochlear Limited Bone Anchored Solutions AB, Mölnlycke, Sweden), functions by using a skin penetrating titanium implant that transmits sound waves to the cochlea through the skull bone. A transcutaneously worn, nonsurgical application of the BAHA is a bone conduction-type hearing aid which utilizes a Headband or Softband. The Headband/Softband consists of an elastic band with a plastic disc-like snap connector sewn into the band. A BAHA sound process is attached to the plastic connector and adjusted to the size of the individual's head, secured with a Velcro® fastener (Velcro USA Inc., Manchester, NH).

This document addresses the use of the BAHA, a U.S. Food and Drug Administration (FDA) approved implantable or transcutaneously worn bone conduction hearing aid as an alternative to an air conduction hearing aid in the treatment of moderate-to-severe hearing loss (HL), or, to improve speech recognition in individuals with unilateral sensorineural hearing loss, also referred to as single sided deafness (SSD™).

Note: Please see the following documents related to implants and hearing aids for the treatment of hearing loss:

- SURG.00014 Cochlear Implants and Auditory Brainstem Implants
- SURG.00084 Implantable Middle Ear Hearing Aids

Note: Benefit language supersedes this document. Hearing aids are not a covered benefit under all member contracts/certificates. Please see the text in the footnote of this document regarding Federal and State mandates and contract language, as these requirements or documents may specifically address the topic of hearing aids.

Position Statement

Medically Necessary:

An implantable bone-anchored hearing aid is considered **medically necessary** for individuals who meet the criteria specified in either (A) **or** (B), below.

A. An implantable bone-anchored hearing aid is considered **medically necessary** as an alternative toan air conduction hearing aid for individuals five years of age and older who meet **both** audiologic and medical condition criteria as follows:
   1. Audiologic criteria (must meet **one**):
      - Bilateral implant: Moderate to severe bilateral symmetric bone conductive or mixed (conductive and sensorineural) hearing loss. Symmetric bone conduction

threshold is defined as less than:

a. 10 decibels (dB) average difference between ears (measured at 0.5, 1, 2, and 4 kilohertz [kHz]), or less than a 15 dB difference at individual frequencies (BAHA Divino™); **or**
b. 10 dB average difference between ears (measured at 0.5, 1, 2, and 3 kHz), or less than a 15 dB difference at individual frequencies (BAHA Cordelle II; BAHA BP100; BAHA Intenso™); **OR**

- Unilateral implant: Conductive or mixed (conductive and sensorineural) hearing loss with pure tone average (PTA) bone conduction hearing threshold better than or equal to 45 dB hearing loss (HL) (BAHA Divino, BAHA BP100), 55 dB HL (BAHA Intenso), or 65 dB HL (BAHA Cordelle II).

2. Medical condition criteria (must meet **at least one**):
   - Congenital or surgically induced ear malformations of the external or middle ear canal (e.g., atresia); **or**
   - Severe chronic external otitis or otitis media; **or**
   - Tumors of the external ear canal or tympanic cavity; **or**
   - Dermatitis of the external ear canal, including reactions from ear molds used in air conduction hearing aids; **or**
   - Other anatomic or medical conditions that contraindicate the use of an air conduction hearing aid.

B. An implantable bone-anchored hearing aid is considered **medically necessary** to improve speech recognition in individuals five years of age and older with unilateral sensorineural hearing loss (i.e. single sided deafness) while the other ear has normal hearing. Normal hearing is defined as PTA air conduction (AC) threshold equal to or better than 20 dB HL at 0.5, 1, 2, and 3 kHz.

C. A transcutaneously worn BAHA (bone conduction-type hearing aid) utilizing a Headband or Softband is considered **medically necessary** as an alternative to an implantable bone anchored hearing aid or air conduction hearing aid in individuals who meet the criteria specified in either (A) **or** (B), above, except for the age limitation of 5 years of age and older which does not apply for a transcutaneously worn BAHA.

Replacement parts or upgrades to existing BAHA components (e.g., batteries, processor, or Headband/Softband) are considered **medically necessary** for individuals whose response to existing componentsis inadequate to the point of interfering with activities of daily living **or** when components are no longer functional.

Not Medically Necessary

Replacement parts or upgrades to existing BAHA components (e.g., batteries, processor, or Headband/Softband) are considered **not medically necessary** when the criteria specified in (A) **or** (B) **or** (C) above are not met **or** when requested for convenience **or** to upgrade to newer technology when the current components remain functional.

Investigational and Not Medically Necessary:

An implantable bone-anchored hearing aid or a transcutaneously worn bone conduction-type hearing aid utilizing a Headband or Softband is considered **investigational and not medically necessary** for all other indications when the above criteria are not met.

Rationale

BAHA for Moderate to Severe Conductive or Mixed Hearing Loss

The medical literature contains numerous prospective and retrospective clinical trials that evaluate

the safety and efficacy of an implanted bone-anchored hearing aid for moderate to severe conductive or mixed hearing loss. Participants in these studies usually received unilateral hearing aids. The early studies of the BAHA (Granstrom, 1997 and 2001; Hakansson, 1990 and 1994) were reported by the BAHA implant programs at the Sahlgrenska Hospital at the University of Göteborg, Sweden (where the BAHA was originally developed); the Nijmegen University Hospital, The Netherlands (Snik, 1995 and 2001; Stenfelt, 2000; van der Pouw, 1998 and 1999); and the Birmingham Osseointegration Program (The Queen Elizabeth, Selly Oak, and Birmingham Children's Hospitals, Birmingham, UK) (Dutt, 2002 [multiple studies]; McDermott, 2002, two studies; McLarnon, 2004). Results from each of the centers are reported in multiple articles with overlapping study populations. The authors suggest that the BAHA can provide significant improvements in functional gain, speech perception, and hearing ability in various listening situations. User satisfaction was also reported in self-assessed outcomes measurements including satisfaction with fit and comfort and with the quality and clarity of the sound. Follow-up in these studies varied widely, ranging from a few weeks or months to more than 20 years.

Most of the early studies from Canada and the United States describing the use of the BAHA were small, retrospective trials where investigators reported positive audiologic outcomes, few complications and high levels of user satisfaction in those who could not tolerate or were not suitable candidates for conventional air conduction hearing aids (Lustig, 2001; Niparko, 2003; Wazen, 1998). Additional case series and reviews have been published that report improved hearing outcomes and functioning in individuals with use of the BAHA. The evidence suggests that the majority of users prefer the BAHA over conventional hearing aids, reporting improved speech recognition scores and sound quality (Christensen, 2010; House, 2010; Ricci, 2011; de Wolf, 2011; Zeitler, 2012). The BAHA is also associated with improvements in language development in children five years of age and older. In a retrospective, treatment outcome study, Lloyd and colleagues (2007) reported that children (n=85 ears, mean age at primary implantation 8.7 years) had "significant additional benefits in terms of speech recognition, sound quality, ease of use, and overall quality of life," despite experiencing adverse outcomes (trauma and failure of osseointegration were the most common reasons for failure) when implanted with the BAHA.

Indications for Bilateral BAHA for Conductive Hearing Loss

The implantation of bilateral BAHA has been evaluated in several small studies. Dutt and colleagues (2002) reported user satisfaction and speech intelligibility in 15 individuals with unilateral BAHA subsequently fitted with a bilateral BAHA. The benefits of bilateral amplification were compared to unilateral amplification in 11 of these individuals who used their second BAHA for 12 months or longer. Following a subjective analysis in the form of comprehensive questionnaires, objective testing was undertaken to assess specific issues such as 'speech recognition in quiet,' 'speech recognition in noise' and a modified 'speech-in-simulated-party-noise' (Plomp) test. 'Speech in quiet' testing revealed a 100% score with both unilateral and bilateral BAHA. With 'speech in noise,' all 11 individuals were reported as scoring "marginally better" with bilateral aids compared to best unilateral responses. A prospective study of 12 individuals reported by Priwin and colleagues (2004) demonstrated a significant improvement in sound localization with bilateral BAHA fitting. Furthermore, the authors reported an improvement in speech reception threshold in both quiet and in noise, concluding that the outcomes with bilateral BAHA were better than with unilaterally fitted BAHA. Bosman and colleagues (2001) evaluated bilateral fittings of the BAHA in 25 individuals with at least three months experience with using two BAHA. The authors reported a significant improvement in directional hearing and speech reception threshold for sentences in quiet ($p<0.01$) for the bilateral fittings compared to the unilateral fittings. Speech recognition in noise was also reported as significantly improved with a second BAHA.

Priwin and colleagues (2007) investigated whether fitting of bilateral BAHA in children with conductive bilateral hearing loss (BHL) provided additional hearing benefits. In this prospective

case series, 22 children (15 controls) were studied with either conductive unaided or with unilateral hearing aid (UHL) or conductive BHL (with unilateral or bilateral BAHA). Baseline audiometry, tone thresholds in a sound field, speech recognition in noise and sound localization were tested with and without unilateral and bilateral hearing aids. The authors reported an additional BAHA in the children with BHL resulted in a tendency to have improved hearing in terms of better sound localization and speech recognition in noise.

The BAHA has been reported as successfully used in children younger than five years of age in Europe and the United Kingdom. However, a 1999 update of the FDA notification lists age less than five years as a contraindication to use of the BAHA. A number of reports describe experience with preschool children or children with developmental issues that might interfere with maintenance of the implant and skin integrity. A two-stage procedure is used in young children with the fixture placed into the bone at the first stage and, after three to six months to allow for osseointegration, a second procedure to connect the abutment through the skin to the fixture. Davids and colleagues (2007) retrospectively compared auditory and speech-language development in 20 children five years of age and younger fitted with the BAHA to a control group of older children (n=20). Children with cortical bone thickness greater than four millimeters underwent a single-stage procedure. The interstage interval for children having two-stage procedures was significantly longer in the study group to allow implantation in younger children without increasing surgical or postoperative morbidity. Two traumatic fractures occurred in the study group versus four in the older children. Three younger children required skin site revision. All children were wearing their BAHA at the time of writing. McDermott and colleagues (2008) reported on the role of the BAHA in 15 children (ages two to 15 years) with Down syndrome in a retrospective case analysis and postal survey of complication rates and quality of life outcomes. All of the children were using their BAHA after follow-up of 14 months. No fixtures were lost; skin problems were encountered in three children. All 15 children were reported as having improved social and physical functioning as a result of improved hearing.

The Health Technology Assessment Program (Colquitt, 2011) published a systematic review of 12 studies on the use of BAHAs for bilateral hearing impairment. No studies with control groups were identified for the review. Cohort pre-post studies and cross-sectional comparative studies demonstrated improvements in hearing with use of BAHAs over conventional bone-conduction hearing aids or unaided hearing. Bilateral use of BAHAs improved hearing outcomes in some individuals over unilateral use, but the evidence was uncertain. Implant loss was noted to be between 6.1% and 19.4%. Improvements in hearing-specific quality of life with BAHAs were found by a hearing-specific instrument, but not general quality of life measures. Overall, adverse events data was limited and the quality of the studies was low. The authors concluded, however, that based on the available evidence, BAHAs appear to be a reasonable treatment option for individuals with bilateral conductive or mixed nearing loss.

Janssen and colleagues (2012) conducted a systematic review to assess the outcomes of bilateral versus unilateral BAHA for individuals with bilateral permanent conductive hearing loss (CHL). Studies were included if subjects of any age had permanent bilateral CHL and bilateral implanted BAHAs. Outcome measures included any subjective or objective audiologic measures, quality of life indicators, or reports of adverse events. Eleven observational studies met the inclusion criteria. In most studies, comparisons between unilateral and bilateral BAHA were intra-subject. Subjects ranged in age from 5 to 83 years of age. Heterogeneity of the methodologies between studies precluded meta-analysis; therefore, the authors performed a qualitative review. Three of the 11 studies were excluded from the qualitative review because some subjects were included in multiple publications. Adverse events were not an outcome measure of any of the included studies. In general, bilateral BAHA was observed to provide additional objective and subjective benefit compared to unilateral BAHA in measures of improvement in tone thresholds associated with bilateral BAHA (range, 2dB to 15dB), improvement in speech recognition patterns (range, 4dB to 5.4dB), and improvement in word recognition scores (range, 1% to 8%). These results, however,

are based on a limited number of small observational studies consisting of heterogeneous study groups that varied in age, severity of hearing loss, etiology of hearing loss, and previous amplification experience.

BAHA for Unilateral Sensorineural Hearing Loss

The BAHA system was cleared by the FDA in 2002 for use in individuals with unilateral sensorineural hearing loss. The BAHA system is intended to improve speech recognition in these individuals with single sided deafness (SSD) and normal hearing in the other ear. Baguley and colleagues (2006) reviewed the evidence for use of a contralateral BAHA in adults with acquired unilateral sensorineural hearing loss. None of the four controlled trials in this meta-analysis reported a significant improvement in auditory localization with the BAHA (Bosman, 2003; Hol, 2004; Niparko, 2003; Wazen, 2003). However, speech discrimination in noise and subjective measures improved with these aids; for these parameters, use of the BAHA resulted in greater improvement than that obtained with the CROS systems. Baguley and colleagues (2006) noted a number of limitations in these studies including bias in terms of participant selection (two studies), all four studies were underpowered, and double reporting of study participant outcomes. Lin and colleagues (2006) reported on use of the BAHA in 23 individuals with unilateral sensorineural hearing loss, and noted that speech recognition in noise was significantly better with the BAHA than with an air conduction CROS. While the report also comments that benefit was seen in those with moderate sensorineural hearing loss in the contralateral ear (25-50 dB), this conclusion was based on only five participants. In a prospective study conducted within a hospital auditory implant center in the United Kingdom, Pai and colleagues (2012) reported significant improvement in the average score in all three sections (speech hearing, spatial hearing, other qualities) of the spatial and qualities of hearing scale SSQ questionnaire following BAHA implantation in 25 adults. To date, the BAHA system has not received FDA clearance for use in individuals with bilateral sensorineural hearing loss.

Indications for the BAHA Headband/Softband

The Headband or Softband for BAHA (FDA, 2000) is a non-surgical application of the hearing aid part of the BAHA intended for use in individuals who meet criteria for moderate to severe mixed bone conductive hearing loss or SSD. The BAHA with Softband has been suggested as a temporary solution for use in younger children until the strength and thickness of the bone of the skull behind the ear allows for surgical implantation of the titanium abutment. For bilateral conductive hearing losses, the BAHA with Softband has been suggested to provide an average of 40.5 dB functional gain across the speech spectrum.

A number of small retrospective case series, comparative studies, and review publications suggest that infants and children under five years of age with bilateral congenital aural atresia (CAA) may benefit from an externally worn BAHA, prior to BAHA implantation (Dun, 2010; Priwin, 2007; Zarowski, 2011). Hol and colleagues (2005) evaluated the validity of a BAHA with Softband (fitted unilaterally and bilaterally) in two young children with severe bilateral conductive hearing loss due to CAA. In a small multicenter comparative study, 12 children (including the two children in the Hol, 2005 article) with bilateral CAA with a pure conductive hearing loss of around 60 dB HL were fitted with the BAHA with Softband (Verhagen, 2008). These children were retrospectively compared to a reference group of eight children selected from a database of those who had a conventional bone conduction hearing aid for bilateral CAA. The authors reported the mean aided hearing threshold of the children with the BAHA with Softband compared to the reference group was 27 dB HL, plus or minus 6 dB HL to 25 dB HL plus or minus 6 dB HL, respectively. Further results compared psychological and language development in five of the 12 children available from the BAHA with Softband group.

Ramakrishnan and colleagues (2011) used the Glasgow Benefit Inventory (GBI) and Listening

Situation Questionnaire to report quality of life findings in a retrospective cross-sectional survey administered to parents of 22 children (n=109 total participants), some with skull and congenital/chromosomal abnormalities from inherited syndromes that involve unilateral (hemifocal microsomia) or bilateral hearing impairment (Treacher-Collins Syndrome, n=4/22) due to microtia or aural atresia. The youngest child utilizing an externally worn BAHA with Softband was six months of age. Overall, parents reported short-term satisfaction in the mean GBI scores for the children after three months of implanted BAHA or externally worn BAHA with Softband use. Despite the heterogeneous etiology of children in the study population, the authors suggest that "The utility of BAHAs for children with syndromes and craniofacial anomalies is poorly recognized, resulting in delays in aid fitting and therefore in early hearing rehabilitation." "In such cases, surgical reconstruction of the ear canal and middle-ear defects is not only technically challenging but also plagued by poor results (with a high rate of ear canal restenosis and limited functional hearing benefit). Hence, alternative treatment options such as Softband and BAHA may be of considerable benefit."

Christensen and colleagues (2010) conducted a retrospective five-year case review of ten children, six months to 16 years of age, with bilateral conductive hearing loss due to CAA and/or microtia who were initially fit with traditional bone-conduction hearing aids, progressed to the externally worn BAHA with Softband, and finally to a unilateral implanted BAHA. The amount of functional gain at 500, 1000, 2000, and 4000 Hz delivered by the various devices was examined as well as the threshold measures with each device at each frequency. The participants showed a statistically significant improvement when using the externally worn BAHA with Softband over traditional bone-conduction hearing aids.

Nicholson and colleagues (2011) retrospectively reviewed cases of 25 children, ages 6 months to 18 years with craniofacial disorders and bilateral conductive hearing loss, who were consistent full-time, externally worn, unilateral BAHA with Softband users as a prerequisite to surgical implantation. The primary study outcome used aided and unaided soundfield audiometric thresholds to measure functional gain. Audibility of the speech spectrum was verified by comparison with target aided thresholds. An analysis of the results revealed an improvement in soundfield thresholds using the BAHA with Softband for the four octave frequencies; percentages of thresholds meeting target levels were significant at all frequencies, exceeding the 80% criterion. The investigators concluded use of the BAHA with Softband provided audibility of the speech spectrum for infants and children with bilateral congenital conductive hearing loss.

In summary, while there are no published, randomized controlled trials comparing the efficacy of an externally worn BAHA with Softband (i.e. bone conduction hearing aid) to an implantable BAHA in measurements of directional hearing, sound localization, and speech recognition in noise, this device may be appropriate for individuals under age five who are not yet appropriate for a surgically implanted device, in particular infants and children with bilateral CAA who cannot be fitted for standard acoustic hearing aids placed in the ear canal.

Background/Overview

Hearing loss can be classified as conductive, sensorineural, or mixed hearing loss. Conductive hearing loss involves the external and middle ear and is due to mechanical or physical blockage of sound as a result of excessive cerumen, a punctured eardrum, birth/congenital defects such as congenital aural atresia (CAA), ear infections or heredity. In sensorineural or "nerve" hearing loss, the auditory cranial nerve or part of the bone of the inner ear is damaged due to birth-related condition, long-term viral or bacterial infections, trauma, exposure to loud noises, the use of certain drugs, fluid buildup in the middle ear, or a benign tumor in the inner ear (acoustic neuroma). Mixed hearing loss is conductive hearing loss coupled with sensorineural hearing loss. Normal range or no impairment of hearing occurs at 0 to 20 dB threshold. The American Speech-Language-Hearing Association (ASLHA, 2010) defines the degree (severity) of hearing loss (HL)

as mild (20 to 40 dB), moderate (40 to 60 dB), severe (60 to 80 dB), and profound (greater than or equal to 80 dB).

Conventional external hearing aids can be generally categorized as air conduction hearing aids or bone conduction hearing aids. Air conduction hearing aids are designed for placement in several locations including fitted behind the ear or on the body (both require the use of an ear mold), in the outer ear, ear canal or almost entirely in the canal, or as a CROS hearing aid where the microphone is located on the impaired hearing side and transmits a signal wirelessly over a radio frequency to the normal hearing ear via an ear mold. Use of ear molds may be problematic in individuals with chronic middle ear and ear canal infections, atresia of the external canal, or an ear canal that cannot accommodate an ear mold. In these individuals, bone conduction hearing aids may be an alternative. External bone conduction hearing aids function by transmitting sound waves through the bone to the ossicles of the middle ear. The external aids must be closely applied to the temporal bone, with either a steel spring over the top of the head or with the use of a spring-loaded arm on a pair of eyeglasses. These hearing aids may be associated with either pressure headaches or soreness.

The FDA approved BAHA system is a bone-anchored, bone conduction hearing aid cleared for use in children ages five years and older and in adults for the following indications:

- Individuals who have conductive or mixed hearing loss and can still benefit from sound amplification;
- Individuals with bilaterally symmetric conductive or mixed hearing loss (may be implanted bilaterally);
- Individuals with sensorineural deafness in one ear and normal hearing in the other (SSD);
- Individuals who are candidates for an air conduction CROS hearing aid but who cannot or will not wear an air conduction CROS hearing aid.

The BAHA processor is coupled to a titanium fixture (screw) protruding through the skin located in the upper mastoid region on the temporal bone where it has fused with the bone in a process called "osseointegration." The BAHA system bypasses the middle ear altogether, sending sound around the area, naturally stimulating the cochlea through bone conduction. The difference between the standard bone conduction hearing aid and the bone-anchored hearing aid is direct stimulation of the bone instead of stimulation through the skin.

There are four BAHA sound processors that have received FDA 510(k) clearance for use with the BAHA auditory osseointegrated implant system: BAHA Cordelle II, BAHA Divino, BAHA Intenso (digital signal processing), and BAHA BP100 (a substantially equivalent processor to predicate models). The BAHA Divino and BP100 are intended for use in individuals with a PTA bone conduction threshold of 45 dB or better (FDA, 2004; FDA, 2009), the BAHA Intenso for individuals with PTA bone conduction threshold of 55 dB or better (FDA, 2008), while the Cordelle II is indicated for more severe hearing loss, with a PTA bone threshold of 65 dB or better (FDA, 2008). In May 2011, the FDA cleared a modified sound processor, the BAHA BP110 Power, as a substantially equivalent device to the predicate BAHA Intenso. According to the manufacturer, the BP110 Power is considered an upgrade to the currently marketed BAHA Intenso and will replace it in the U.S. market. The BAHA BP110 Power improvements in features and amplified sound processing are the same as those used in another BAHA processor that has already been cleared for marketing for a less hearing-impaired population (the model BP100, cleared under K090720).

Implantable or bone-anchored conduction hearing aids are recommended for individuals who are unable to use conventional air conduction hearing aids or have undergone ossicular replacement surgery because of chronic otitis media, congenital malformation of the middle/external ear or other acquired malfunctions of the middle or external ear canals which preclude wearing of a

conventional air conduction hearing aid. Consideration should be given to the individual's psychological, physical, emotional and developmental capabilities of maintaining hygiene as the skin is adjacent to the implant abutment. For children and individuals with congenital malformations, sufficient bone volume and bone quality must be present for a successful fixture implantation.

The Headband/Softband for BAHA received FDA 510(k) clearance in October 2000 as substantially equivalent to devices already on the market. The Headband/Softband consists of an elastic band with a plastic disc-like snap connector sewn into the band. A BAHA sound process is attached to the plastic connector and adjusted to the size of the individual's head, secured with a Velcrofastener. The sound processor is held against the skin behind the ear, or at another bony location of the skull, through pressure from the band. In this application there is no implantation surgery of an abutment into the skull. The Headband/Softband functions in the same manner as a conventional bone conduction hearing aid, with the amplified vibrational sounds transmitted transcutaneously to the bones of the skull for transmission to the cochlea. The signal is weakened as it passes through the skin (attenuation). The manufacturer of the BAHA system cautions against use of the Softband during the titanium implant/fixture healing process. The sound processor must not be placed on top of the abutment/implant as it may jeopardize osseointegration. In addition, the Softband contains natural rubber latex that may cause an allergic reaction in some individuals.

Definitions

Conductive hearing loss: Hearing loss that occurs when sound is conducted inefficiently through the outer ear canal to the eardrum and the small bones (ossicles) of the middle ear; involves a reduction in sound level or the ability to hear faint sounds.

Congenital aural atresia (CAA): A rare spectrum of congenital deformities present at birth that involve some degree of failure of the development of the external auditory canal; commonly accompanied by abnormalities of both the middle ear bones in various degrees, as well as the external ear, including microtia (i.e. small ear) or incomplete development of the auricle (the outer projecting portion of the ear).

Decibel (dB): A unit for expressing the loudness of sound.

Hearing loss (HL): Any degree of impairment of the ability to apprehend sound.

Hertz (Hz): A unit of frequency equivalent to 1 cycle per second.

Mixed hearing loss: Hearing loss that is both conductive and sensorineural, occurring in one or both ears.

Otitis: Inflammation or infection of the ear.

Pure tone average (PTA): The average of hearing sensitivity at 0.5, 1, 2, and 3 kHz.

Sensorineural hearing loss: A permanent hearing loss related to the sensory or neural structures responsible for hearing that involves a reduction in sound level or ability to hear faint sounds; affects speech understanding or the ability to hear clearly; the involved structures include, but are not limited to, the cochlea and the acoustic nerve.

Single sided deafness (SSD): Significant or total hearing loss in one ear; also known as unilateral sensorineural hearing loss. SSD may be a result of surgery to treat acoustic neuroma or other tumors of the eighth cranial nerve.

Temporal bone: A bone located on the side of the head that is part of the skull.

Transcutaneous: Refers to a device or medication applied directly to unbroken skin.

Tympanic membrane: The membrane in the ear that vibrates to sound; referred to as the eardrum.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. A draft of future ICD-10 Coding (effective 10/01/2014) related to this document, as it might look today, is included below for your reference. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

69710	Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone
69714	Implantation, osseointegrated implant, temporal bone, with percutaneous attachment to external speech processor/cochlear stimulator; without mastoidectomy
69715	Implantation, osseointegrated implant, temporal bone, with percutaneous attachment to external speech processor/cochlear stimulator; with mastoidectomy
69717	Replacement (including removal of existing device), osseointegrated implant, temporal bone, with percutaneous attachment of external speech processor cochlear stimulator; without mastoidectomy
69718	Replacement (including removal of existing device), osseointegrated implant, temporal bone, with percutaneous attachment of external speech processor cochlear stimulator; with mastoidectomy

HCPCS

L8690	Auditory osseointegrated device, includes all internal and external components
L8691	Auditory osseointegrated device, external sound processor, replacement
L8692	Auditory osseointegrated device, external sound processor; used without osseointegration, body worn, includes headband or other means of external attachment [when specified as BAHA Headband or Softband device]
L8693	Auditory osseointegrated device, abutment, any length, replacement only

ICD-9 Procedure

20.95	Implantation of electromagnetic hearing device

ICD-9 Diagnosis

380.10	Infective otitis externa, unspecified
380.15-380.16	Chronic mycotic, other chronic infective otitis externa
380.21-380.23	Other otitis externa
380.50-380.53	Acquired stenosis of external ear canal
381.10-381.4	Chronic serous, mucoid other otitis media
382.1-382.9	Chronic suppurative otitis media
384.20-384.25	Perforation of tympanic membrane
385.00-385.9	Other disorders of middle ear and mastoid
389.00-389.9	Hearing loss
744.00-744.09	Anomalies of ear causing impairment of hearing

ICD-10 Procedure	***ICD-10-PCS draft codes; effective 10/01/2014:***
09HD04Z-09HD44Z	Insertion of bone conduction hearing device into right inner ear [by approach; includes codes 09HD04Z, 09HD34Z, 09HD44Z]
09HE04Z-09HE44Z	Insertion of bone conduction hearing device into left inner ear [by approach; includes codes 09HE04Z, 09HE34Z, 09HE44Z]
09HD0SZ-09HD4SZ	Insertion of hearing device into right inner ear [by approach; includes codes 09HD0SZ, 09HD3SZ, 09HD4SZ]
09HE0SZ-09HE4SZ	Insertion of hearing device into left inner ear [by approach; includes codes 09HE0SZ, 09HE3SZ, 09HE4SZ]
0NH50SZ-0NH54SZ	Insertion of hearing device into right temporal bone [by approach; includes codes 0NH50SZ, 0NH53SZ, 0NH54SZ]
0NH60SZ-0NH64SZ	Insertion of hearing device into left temporal bone [by approach; includes codes 0NH60SZ, 0NH63SZ, 0NH64SZ]

ICD-10 Diagnosis	***ICD-10-CM draft codes; effective 10/01/2014:***
H60.311-H60.329	Diffuse/hemorrhagic otitis externa
H60.391-H60.399	Other infective otitis externa
H60.40-H60.43	Cholesteatoma of external ear
H60.501-H60.599	Acute noninfective otitis externa
H60.60-H60.63	Unspecified chronic otitis externa
H60.8X1-H60.8X9	Other otitis externa
H60.90-H60.93	Unspecified otitis externa
H61.301-H61.399	Acquired stenosis of external ear canal
H65.20-H65.23	Chronic serous otitis media
H65.30-H65.33	Chronic mucoid otitis media
H65.411-H65.499	Other chronic nonsuppurative otitis media
H65.90-H65.93	Unspecified nonsuppurative otitis media
H66.10-H66.23	Chronic tubotympanic/atticoantral suppurative otitis media
H66.3X1-H66.3X9	Other chronic suppurative otitis media
H66.40-H66.43	Suppurative otitis media, unspecified
H66.90-H66.93	Otitis media, unspecified
H71.00-H71.93	Cholesteatoma of middle ear
H72.00-H72.93	Perforation of tympanic membrane
H74.01- H74.93	Other disorders of middle ear mastoid
H90.0-H90.8	Conductive and sensorineural hearing loss
H91.01-H91.09	Ototoxic hearing loss
H91.10-H91.13	Presbycusis
H91.20-H91.23	Sudden idiopathic hearing loss
H91.8X1-H91.8X9	Other specified hearing loss
H91.90-H91.93	Unspecified hearing loss
Q16.0-Q16.9	Congenital malformations of ear causing impairment of hearing

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met; for all other diagnoses, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

References

Peer Reviewed Publications:

1. Baguley DM, Bird J, Humphriss RL, Prevost AT. The evidence base for the application of contralateral bone anchored hearing aids in acquired unilateral sensorineural hearing loss in

adults. Clin Otolaryngol. 2006; 31(1):6-14.
2. Bosman AJ, Hol MK, Snik AF, et al. Bone-anchored hearing aids in unilateral inner ear deafness. Acta Otolaryngol. 2003; 123(2):258-260.
3. Christensen L, Smith-Olinde L, Kimberlain J, et al. Comparison of traditional bone-conduction hearing AIDS with the Baha system. J Am Acad Audiol. 2010; 21(4):267-273.
4. Colquitt JL, Jones J, Harris P, et al. Bone-anchored hearing aids (BAHAs) for people who are bilaterally deaf: a systematic review and economic evaluation. Health Technol Assess. 2011; 15(26):1-200, iii-iv.
5. Davids T, Gordon KA, Clutton D, et al. Bone-anchored hearing aids in infants and children younger than 5 years. Arch Otolaryngol Head Neck Surg. 2007; 133(1):51-55.
6. de Wolf MJ, Hendrix S, Cremers CW, Snik AF. Better performance with bone-anchored hearing aid than acoustic devices in patients with severe air-bone gap. Laryngoscope. 2011; 121(3):613-616.
7. Dun CA, de Wolf MJ, Mylanus EA, et al. Bilateral bone-anchored hearing aid application in children: the Nijmegen experience from 1996 to 2008. Otol Neurotol. 2010; 31(4):615-623.
8. Dutt SN, McDermott AL, Burrell SP, et al. Patient satisfaction with bilateral bone-anchored hearing aids: the Birmingham experience. J Laryngol Otol Suppl. 2002; (28):37-46.
9. Dutt SN, McDermott AL, Burrell SP, et al. Speech intelligibility with bilateral bone-anchored hearing aids: the Birmingham experience. J Laryngol Otol Suppl. 2002; (28):47-51.
10. Dutt SN, McDermott AL, Jelbert A, et al. Day to day use and service-related issues with the bone-anchored hearing aid: the Entific Medical Systems questionnaire. J Laryngol Otol Suppl. 2002; (28):20-28.
11. Dutt SN, McDermott AL, Jelbert A, et al. The Glasgow benefit inventory in the evaluation of patient satisfaction with the bone-anchored hearing aid: quality of life issues. J Laryngol Otol Suppl. 2002; (28):7-14.
12. Granstrom G, Bergstrom K, Odersjo M, Tjellstrom A. Osseointegrated implants in children: experience from our first 100 patients. Otolaryngol Head Neck Surg. 2001; 125(1):85-92.
13. Granstrom G, Tjellstrom A. The bone-anchored hearing aid (BAHA) in children with auricular malformations. Ear Nose Throat J. 1997; 76(4):238-247.
14. Hakansson BE, Carlsson PU, Tjellstrom A, Liden G. The bone-anchored hearing aid: principal design and audiometric results. Ear Nose Throat J. 1994; 73(9):670-675.
15. Hakansson BE, Liden G, Tjellstrom A, et al. Ten years of experience with the Swedish bone-anchored hearing system. Ann Otol Rhinol Laryngol Suppl. 1990; 151:1-16.
16. Hol MK, Bosman AJ, Snik AF, et al. Bone-anchored hearing aid in unilateral inner ear deafness: a study of 20 patients. Audiol Neurootol. 2004; 9(5):274-281.
17. Hol MK, Cremers CW, Coppens-Schellekens W, Snik AF. The BAHA Softband. A new treatment for young children with bilateral congenital aural atresia. Int J Pediatr Otorhinolaryngol. 2005; 69(7):973-980.
18. House JW, Kutz JW Jr, Chung J, Fisher LM. Bone-anchored hearing aid subjective benefit for unilateral deafness. Laryngoscope. 2010; 120(3):601-617.
19. Janssen RM, Hong P, Chadha NK. Bilateral bone-anchored hearing aids for bilateral permanent conductive hearing loss: a systematic review. Otolaryngol Head Neck Surg. 2012; 147(3):412-422.
20. Lin L, Bowditch S, Anderson M, et al. Amplification in the rehabilitation of unilateral deafness: Speech in noise and directional hearing effects with bone-anchored hearing and contralateral routing of signal amplification. Otol Neurotol. 2006; 27(2):172-182.
21. Lloyd S, Almeyda J, Sirimanna KS, et al. Updated surgical experience with bone-anchored hearing aids in children. J Laryngol Otol. 2007: 121(9):826-831.
22. Lustig LR, Arts HA, Brackmann DE, et al. Hearing rehabilitation using the BAHA bone-anchored hearing aid: results in 40 patients. Otol Neurotol. 2001; 22(3):328-334.
23. McDermott AL, Dutt SN, Reid AP, Proops DW. An intra-individual comparison of the previous conventional hearing aid with the bone-anchored hearing aid: the Nijmegen group questionnaire. J Laryngol Otol Suppl. 2002; (28):15-19.
24. McDermott AL, Dutt SN, Tziambazis E, et al. Disability, handicap and benefit analysis with

the bone-anchored hearing aid: the Glasgow hearing aid benefit and difference profiles. J Laryngol Otol Suppl. 2002; (28):29-36.
25. McDermott AL, Williams J, Kuo MJ. The role of bone anchored hearing aids in children with Down syndrome. Int J Pediatr Otorhinolaryngol. 2008; 72(6):751-757.
26. McLarnon CM, Davison T, Johnson IJ. Bone-anchored hearing aid: comparison of benefit by patient subgroups. Laryngoscope. 2004; 114(5):942-944.
27. Nicholson N, Christensen L, Dornhoffer J, et al. Verification of speech spectrum audibility for pediatric baha softband users with craniofacial anomalies. Cleft Palate Craniofac J. 2011; 48(1):56-65.
28. Niparko JK, Cox KM, Lustig LR. Comparison of the bone anchored hearing aid implantable hearing device with contralateral routing of offside signal amplification in the rehabilitation of unilateral deafness. Otol Neurotol. 2003; 24(1):73-78.
29. Pai I, Kelleher C, Nunn T, et al. Outcome of bone-anchored hearing aids for single-sided deafness: a prospective study. Acta Otolaryngol. 2012; 132(7):751-755.
30. Priwin C, Jönsson R, Hultcrantz M, Granström G. BAHA in children and adolescents with unilateral or bilateral conductive hearing loss: a study of outcome. Int J Pediatr Otorhinolaryngol. 2007; 71(1):135-145.
31. Priwin C, Stenfelt S, Granström G, et al. Bilateral bone-anchored hearing aids (BAHAs): an audiometric evaluation. Laryngoscope. 2004; 114(1):77-84.
32. Ramakrishnan Y, Marley S, Leese D, et al. Bone-anchored hearing aids in children and young adults: the Freeman Hospital experience. J Laryngol Otol. 2011; 125(2):153-157.
33. Ricci G, Volpe AD, Faralli M, et al. Bone-anchored hearing aids (Baha) in congenital aural atresia: personal experience. Int J Pediatr Otorhinolaryngol. 2011; 75(3):342-346.
34. Snik AF, Mylanus EA, Cremers CW. The bone-anchored hearing aid compared with conventional hearing aids. Audiologic results and the patients' opinions. Otolaryngol Clin North Am. 1995; 28(1):73-83.
35. Snik AF, Mylanus EA, Cremers CW. The bone-anchored hearing aid: a solution for previously unresolved otologic problems. Otolaryngol Clin North Am. 2001; 34(2):365-372.
36. Stenfelt S, Hakansson B, Jonsson R, Granstrom G. A bone-anchored hearing aid for patients with pure sensorineural hearing impairment: a pilot study. Scand Audiol. 2000; 29(3):175-185.
37. van der Pouw CT, Carlsson P, Cremers CW, Snik AF. A new more powerful bone-anchored hearing aid: first results. Scand Audiol. 1998; 27(3):179-182.
38. van der Pouw CT, Mylanus EA, Cremers CW. Percutaneous implants in the temporal bone for securing a bone conductor: surgical methods and results. Ann Otol Rhinol Laryngol. 1999; 108(6):532-536.
39. van der Pouw CT, Snik AF, Cremers CW. The BAHA HC 200/300 in comparison with conventional bone conduction hearing aids. Clin Otolaryngol Allied Sci. 1999; 24(3):171-176.
40. Verhagen CV, Hol MK, Coppens-Schellekens W, et al. The Baha Softband. A new treatment for young children with bilateral congenital aural atresia. Int J Pediatr Otorhinolaryngol. 2008; 72(10):1455-1459.
41. Wazen JJ, Caruso M, Tjellstrom A. Long-term results with the titanium bone-anchored hearing aid: the U.S. experience. Am J Otol. 1998; 19(6):737-741.
42. Wazen JJ, Spitzer JB, Ghossaini SN, et al. Transcranial contralateral cochlear stimulation in unilateral deafness. Otolaryngol Head Neck Surg. 2003; 129(3):248-254.
43. Zarowski AJ, Verstraeten N, Somers T, et al. Headbands, testbands and softbands in preoperative testing and application of bone-anchored devices in adults and children. Adv Otorhinolaryngol. 2011; 71:124-131.
44. Zeitler DM, Snapp HA, Telischi FF, Angeli SI. Bone-anchored implantation for single-sided deafness in patients with less than profound hearing loss. Otolaryngol Head Neck Surg. 2012; 147(1):105-111.

Government Agency, Medical Society, and Other Authoritative Publications:

1. U.S. Food and Drug Administration (FDA) 510(k) Premarket Notification Database. Summary of Safety and Effectiveness. Rockville, MD: FDA. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. Accessed on June 28, 2013:
    - BAHA® BP100. No. K090720. June 17, 2009.
    - BAHA BP110 Power. No. K110996. May 10, 2011.
    - BAHA® Cordelle II. No. K080363. April 10, 2008.
    - BAHA™ for Single Sided Deafness. No. K021837. August 30, 2002.
    - BAHA® Intenso™. No. K081606. August 28, 2008.
    - Bilateral Fitting of BAHA™. No. K011438. July 23, 2001.
    - Branemark Bone-Anchored Hearing Aid (BAHA™) System. No. K984162. June 28, 1999.
    - Headband for BAHA™. No. K002913. October 17, 2000.

Web Sites for Additional Information

1. American Speech-Language-Hearing Association (ASLHA). Types of hearing loss. Available at: http://www.asha.org/public/hearing/disorders/types.htm. Accessed on June 28, 2013.
2. National Institute on Deafness and Other Communication Disorders (NIDCD). Hearing aids. Available at: http://www.nidcd.nih.gov/staticresources/health/hearing/HearingAids07.pdf. Accessed on June 28, 2013.
3. National Institute on Deafness and Other Communication Disorders (NIDCD). Vestibular schwannoma (acoustic neuroma) and neurofibromatosis. Available at: http://www.nidcd.nih.gov/health/hearing/acoustic_neuroma.asp. Accessed on June 28, 2013.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/08/2013	Medical Policy & Technology Assessment Committee (MPTAC) review. Minor format changes throughout document. Updated Rationale, Background, References, and Web Sites for Additional Information sections.
Reviewed	08/09/2012	MPTAC review. Updated Rationale, Background, Coding, References, and Index.
Revised	08/18/2011	MPTAC review. Revised medically necessary age-related criterion for transcutaneously worn BAHA with Softband and investigational and not medically necessary statement for implantable and transcutaneously worn BAHA in individuals who do not meet the criteria in the medically necessary indications. Updated Rationale, Background, Definitions, and References.
Reviewed	02/17/2011	MPTAC review. Updated Description, Rationale, Definitions, and References.

	01/01/2011	Updated Coding section with 01/01/2011 HCPCS changes.
Revised	02/25/2010	MPTAC review. Added a Note addressing hearing aid contract/benefit language to the Description section. Added medically necessary criteria for the Headband/Softband for BAHA and criteria for replacement parts or upgrades to existing BAHA components or Headband/Softband. Added not medically necessary criteria for replacement parts or upgrades to existing BAHA components or Headband/Softband. Added Headband/Softband for BAHA to the investigational and not medically necessary criteria for all other indications. Updated Description, Rationale, Discussion, Coding, and References.
Revised	11/19/2009	MPTAC review. Added FDA 510(k) substantially equivalent sound processor, the BAHA BP100, to the medically necessary Audiologic criteria specific to bilateral and unilateral bone-anchored hearing aids. Updated Rationale, Background, Index, and References. Added Web Sites for Additional Information.
Revised	11/20/2008	MPTAC review. Revised Position Statements to include the FDA-approved BAHA Intenso™. Clarified Audiologic criteria for bilateral implants. Updated Description, Background, Index, and References updated
Revised	08/28/2008	MPTAC review. Revised document title to Bone-Anchored Hearing Aids. Revised medically necessary Audiologic criteria to include separate bilateral or unilateral implant indications based on updated FDA-approval criteria for the BAHA. Clarified medically necessary statement for unilateral sensorineural hearing loss. Updated Description, Rationale, Definitions, Index and References.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	08/23/2007	MPTAC review. Position Statement clarified. Rationale, Background, Definitions, and References updated.
	01/01/2007	Updated Coding section with 01/01/2007 CPT/HCPCS changes.
Revised	09/14/2006	MPTAC review. Revision based on additional FDA criteria for the BAHA System. References and Coding updated.
Reviewed	07/25/2006	MPTAC review.
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations

	Last Review Date	Document Number	Title
Anthem, Inc.	04/28/2005	SURG.00020	Bone-Anchored, Bone Conduction Hearing Device, Implantable
WellPoint Health Networks, Inc.	09/23/2004	2.03.13	Implantable Bone Conduction Hearing Aids

Physical Therapy for Urinary Incontinence

Question: Should physical therapy CPT codes (CPT 97001, 97002, 97110, 97140, 97530) be added to line 471 UTERINE PROLAPSE; CYSTOCELE?

Question source: West Portland Physical Therapy Clinic

Issue: GN 50, which accompanies line 471, calls out physical therapy as one of two modalities which need to be tried prior to surgery for pelvic floor issues/incontinence. However, there are no PT CPT codes on line 471. The PT requirement in GN50 has been reviewed, most recently in June, 2012 and the HERC expressed intent to have PT as a treatment option if possible for incontinence. However, the codes have not been specifically addressed.

From West Portland Physical Therapy Clinic:

I was referred to you by DMAP regarding confusion that we are experiencing regarding the Prioritized List….

We have a female patient with the following conditions:
Covered in Line 492:

618.01: Cystocele, midline
618.82: Incompetence or weakening of rectovaginal tissue
618.9: Unspecified genital prolapse

Line 492 is cross referenced to Guideline Note 50.
Guideline Note 50 states, among other things:

E) Patient required to have 3 months of alternative therapy (e.g., pessaries or **physical therapy**, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, **physical therapist** or trained staff, and have documented consistent practice of these techniques over the 3 month period.

The problem is that there are no physical therapy codes (97001, 97002, 97110, 97140, 97530) that are paired with Line 492 or Line 444.

So here is the dilemma: How can OHP require 3 months of alternative physical therapy prior to consideration of a surgical procedure, yet not cover the physical therapy? This seems absurd and counter-intuitive to funding lower-cost, less-invasive procedures.

We have physical therapist specifically trained on Women's Health Pelvic Floor Rehab who have amazing success with treating conditions such as this within 6 – 8 physical therapy visits with a total cost to the state of approximately $500.00…much less than a surgical procedure!

The concept of requiring alternative care prior to a surgical procedure is a very valid and proven concept. However, in order for it to work the health plan needs to cover the alternative therapy.

GUIDELINE NOTE 50, PELVIC ORGAN PROLAPSE SURGERY

Line 471

Hysterectomy, cystocele repair, and/or other surgery for pelvic organ prolapse may be indicated when all of the following are documented (A-E):

A) Patient history of symptoms of pelvic prolapse such as:
   1) Complaints of the pelvic organs prolapsing at least to the introitus, and one or more of the following:
      a) Low back discomfort or pelvic pressure, or
      b) Difficulty in defecating, or
      c) Difficulty in voiding
B) For hysterectomy
   1) Nonmalignant cervical cytology, if cervix is present, and
   2) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
C) Physical examination is consistent with patient's symptoms of pelvic support defects indicating either symptomatic prolapse of the cervix, enterocele, cystocele, rectocele or prolapse of the vaginal vault
D) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized
E) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period

The similar GN47 refers to line 459, which does include 3 physical therapy CPT codes (97001, 97002, and 97110), but not all the requested CPT codes.

GUIDELINE NOTE 47, URINARY INCONTINENCE

Line 459

Surgery for genuine stress urinary incontinence may be indicated when all of the following are documented (A-G):
A) Patient history of (1, 2, and 3):
   1) Involuntary loss of urine with exertion
   2) Identification and treatment of transient causes of urinary incontinence, if present (e.g., delirium, infection, pharmaceutical causes, psychological causes, excessive urine production, restricted mobility, and stool impaction)
   3) Involuntary loss of urine on examination during stress (provocative test with direct visualization of urine loss) and low or absent post void residual
B) Patient's voiding habits
C) Physical or laboratory examination evidence of either (1 or 2):
   1) Urethral hypermobility
   2) Intrinsic sphincter deficiency
D) Diagnostic workup to rule out urgency incontinence
E) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized
F) Nonmalignant cervical cytology, if cervix is present
G) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

Physical Therapy for Urinary Incontinence

HERC staff recommendations:

1) Add PT services to line 471 UTERINE PROLAPSE; CYSTOCELE
    a. 97001 Physical therapy evaluation
    b. 97002 Physical therapy re-evaluation
    c. 97110 Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
    d. 97140 Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
    e. 97530 Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes
2) Add additional PT services to line 459 URINARY INCONTINENCE
    a. 97140, 97530
3) Add line 471 to the Rehabilitation Guideline
    a. GUIDELINE NOTE 6, REHABILITATIVE THERAPIES
    Lines 34,50,61,72,75,76,78,85,95,96,135,136,140,154,157,164,182,187,188,199,200, 204,205,211,258,260,275,290,292,297,305,306,315,322,345,349,351,358,359,362,374, 380,381,391,410,412,420,422,427,435,447,459,468,471,472,484,492,504,515,533,545, 560,577,579,588,597,616

Section 3.0

Previously Discussed Items

Electroconvulsive therapy (ECT)

Question: For what conditions should electroconvulsive therapy (ECT) be a covered therapy? Should limitations be placed on the length of treatment?

Question source: OHP Medical Directors and DMAP Mental Health Division

Issue: ECT (CPT 90870) is currently on lines 7 MAJOR DEPRESSION, RECURRENT; MAJOR DEPRESSION, SINGLE EPISODE, SEVERE and 29 BIPOLAR DISORDERS. Guideline Note 102 addresses the use of ECT for treatment of depression. There is no guideline addressing its use in bipolar disorder. The OHP medical directors and the mental health division have asked HERC for guidance on the indications and length of therapy for ECT.

This topic was discussed at the May, 2014 VBBS meeting. At that time, HERC staff was directed to consult experts in the field for further assistance on guideline development. Dr. Keepers, head of OHSU Psychiatry Department and practitioner of ECT, has given staff materials and suggestions for the guideline.

Note: vagal nerve stimulation as a non-pharmacologic intervention for depression was reviewed in 2012 and suggested for non-coverage in the HERC coverage guidance issues on this topic. CPT 64658 is on 2 lines (178 Epilepsy, 446 Nerve disorders) but not on the depression line (7)

Current guideline

GUIDELINE NOTE 102, NON-PHARMACOLOGIC INTERVENTIONS FOR TREATMENT-RESISTANT DEPRESSION

Line 7

Repetitive transcranial magnetic stimulation (CPT 90867-90868) and electroconvulsive therapy (CPT 90870) are covered only after failure of at least two antidepressants.

Evidence

1) **Tharyan 2009,** Cochrane review of ECT for schizophrenia
    a. N=26 trials of ECT vs placebo or sham ECT
    b. There was a suggestion that ECT resulted in less relapses in the short term than sham ECT (n=47, 2 RCTs, RR fixed 0.26 CI 0.03 to 2.2), and a greater likelihood of being discharged from hospital (n=98, 1 RCT, RR fixed 0.59, CI 0.34 to 1.01). There is no evidence that this early advantage for ECT is maintained over the medium to long term
    c. When ECT is directly compared with antipsychotic drug treatments (total n=443, 10 RCTs) results favour the medication group (n= 175, 3 RCTs, RR fixed 'not improved at the end of ECT course' 2.18 CI 1.31 to 3.63). Limited evidence suggests that ECT

combined with antipsychotic drugs results in greater improvement in mental state (n= 40, 1 RCT, WMD, Brief Psychiatric Rating Scale -3.9 CI - 2.28 to -5.52) than with antipsychotic drugs alone.

d. When continuation ECT was added to antipsychotic drugs, the combination was superior to the use of antipsychotics alone (n=30, WMD Global Assessment of Functioning 19.06 CI 9.65 to 28.47), or CECT alone (n=30, WMD -20.30 CI -11.48 to -29.12).
e. Authors' conclusions The evidence in this review suggests that ECT, combined with treatment with antipsychotic drugs, may be considered an option for people with schizophrenia, particularly when rapid global improvement and reduction of symptoms is desired. This is also the case for those with schizophrenia who show limited response to medication alone. Even though this initial beneficial effect may not last beyond the short term, there is no clear evidence to refute its use for people with schizophrenia. regarding its role in the management of people with schizophrenia.

1) **NICE 2010**, guidance for the use of ECT
   a. It is recommended that electroconvulsive therapy (ECT) is used only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening, in individuals with
      i. severe depressive illness
      ii. catatonia
      iii. a prolonged or severe manic episode.
   b. The decision as to whether ECT is clinically indicated should be based on a documented assessment of the risks and potential benefits to the individual, including: the risks associated with the anaesthetic; current co-morbidities; anticipated adverse events, particularly cognitive impairment; and the risks of not having treatment.
   c. Clinical status should be assessed following each ECT session and treatment should be stopped when a response has been achieved, or sooner if there is evidence of adverse effects. Cognitive function should be monitored on an ongoing basis
   d. It is recommended that a repeat course of ECT should be considered under the circumstances indicated in 1.1 only for individuals who have severe depressive illness, catatonia or mania and who have previously responded well to ECT. In patients who are experiencing an acute episode but have not previously responded, a repeat trial of ECT should be undertaken only after all other options have been considered and following discussion of the risks and benefits with the individual and/or where appropriate their carer/advocate.

e. As the longer-term benefits and risks of ECT have not been clearly established, it is not recommended as a maintenance therapy in depressive illness.

Other policies

1) **NY state 2012** (utilizes APA 2002 guidelines)
    a. Use of Electroconvulsive Therapy
        i. ECT may be considered as a *primary treatment (or first-line treatment)* for persons exhibiting syndromes such as: severe major depression, acute mania, mood disorders with psychotic features, and catatonia. A decision to use ECT as the primary therapy should be based on an evaluation of the nature and the severity of acute symptoms in conjunction with an evaluation of risks and benefits. ECT may be the initial treatment of choice when a rapid or a higher probability of response is necessary. ECT may also be considered as a primary treatment when there is a history of good response to ECT treatment and/or poor response to alternate treatments during prior episodes.
        ii. ECT is most often used as a *secondary treatment* when a patient has shown insufficient improvement with prescribed treatment(s), which usually includes pharmacotherapy. In addition to lack of substantial clinical response, other reasons to use ECT include, intolerance to side effects of medication or other treatments, deterioration in condition, or appearance of suicidality or pronounced lethargy. In the context of referral for ECT, patients who have not responded to psychotherapy alone should not be considered as having a treatment resistant mental illness - regardless of diagnosis.
        iii. ECT is generally used to treat several *principal diagnostic indications* including major depression, mania, and schizophrenia and may be used for *other diagnostic indications* including psychiatric syndromes associated with medical conditions and medical disorders. (APA pp. 8-22)
        iv. Even when no mental illness is diagnosed, other diagnostic indications may include medical disorders such as: Parkinson's disease, intractable seizure disorder and neuroleptic malignant
        v. The frequency and number of treatments need to be determined by the severity of illness and by the relative benefits and risks of ECT treatment. (APA pgs, 174-177)
    b. Evaluation of Treatment Outcome

i. During the course of ECT, it is important to monitor therapeutic responses and adverse effects of treatment. (APA pp. 197-202)
ii. **Guidelines**: Providers should address requirements for clinical assessments performed by the attending psychiatrist or designee. Assessment should occur prior to ECT and after every one or two treatments, usually within 24 hours after treatment. Formal clinical rating instruments are available and may be employed in documenting therapeutic responses and changes in symptoms. Policies should also discuss the need to determine whether ECT should be continued, reduced in frequency, or suspended when hypo-mania or mania emerges during an ECT course.
iii. During the course of treatment, monitoring should include the presence and severity of disorientation, anterograde amnesia (by use of objective measures), treatment emergent mania, etc. and should also include patient self-reporting. Assessment of orientation and memory should be completed before the initial ECT treatment and at least weekly throughout the treatment course. If disorientation or memory loss are substantial during treatment, modifications to the ECT procedure (from bilateral to right unilateral electrode placement, decrease in electrical intensity, longer intervals between treatments, altering dosage of medications, etc.) may be warranted.
iv. Before each scheduled treatment session, evaluations should address other identified adverse effects that may increase risks during treatment.

2) Nebraska Medicaid 2009

a. The specified requirements for severity of need and intensity and quality of service must be met to satisfy the criteria for outpatient electroconvulsive therapy (ECT).
b. **I. Severity of Need**
i. Criteria A, B, C, D, E and F must be met to satisfy the criteria for severity of need.
1. The clinical evaluation indicates that the patient has a DSM-IV Axis I diagnosis or condition that, by accepted medical standards, can be expected to improve significantly through medically necessary and appropriate ECT. Such diagnoses and conditions include, but are not limited to, Major Depression, Bipolar Disorder, Mood Disorder with Psychotic Features, Catatonia, Schizoaffective Disorder, Schizophrenia, Acute Mania, severe lethargy due to a psychiatric condition, and/or psychiatric syndromes

associated with medical conditions and medical disorders.

2. The type and severity of the behavioral health symptoms are such that a rapid response is required, including, but not limited to, high suicide or homicide risk, extreme agitation, life-threatening inanition, catatonia, psychosis, and/or stupor.
3. Either:
    a. the patient has a history of inadequate response to multiple adequate trials of medications and/or combination treatments, including polypharmacy when indicated, for the diagnosis(es) and condition(s); *or*
    b. the patient is unable or unwilling to comply with or tolerate side effects of available medications, or has a co-morbid medical condition that prevents the use of available medications, such that efficacious treatment with medications is unlikely; *or*
    c. the patient has a history of good response to ECT during an earlier episode of the illness, *or*
    d. the patient is pregnant and has severe mania or depression, and the risks of providing no treatment outweigh the risks of providing ECT.
4. The patient's status and/or co-morbid medical conditions do not rule out ECT; for example; unstable or severe cardiovascular disease, aneurysm or vascular malformation, severe hypertension, increased intracranial pressure, cerebral infarction, cerebral lesions, pulmonary insufficiency, musculoskeletal injuries or abnormalities (e.g., spinal injury), severe osteoporosis, glaucoma, retinal detachment, and/or medical status rated as severe.
5. All:
    a. the patient is medically stable and does not require the 24-hour medical/nursing monitoring or procedures provided in a hospital level of care, *and*
    b. the patient has access to a suitable environment and professional and/or social supports after recovery from the procedure, e.g., one or more responsible caregivers to drive the patient home after the procedure and provide post procedural care and monitoring, especially during the index ECT course, *and*

c. the patient can be reasonably expected to comply with post-procedure recommendations that maintain the health and safety of the patient and others, e.g., prohibition from driving or operating machinery, complying with dietary, bladder, bowel, and medication instructions, and reporting adverse effects and/or negative changes in medical condition between treatments.
d. The patient and/or a legal guardian is able to understand the purpose, risks and benefits of ECT, and provides consent.

3) **British Columbia (undated),** (uses APA 2002 guidelines)
   a. Primary Indications for Use
      i. As stated in the APA guidelines1, there is "compelling data . . . or strong consensus" supporting the use of ECT in the following conditions:
         1. Major Depressive Episode (arising from unipolar depression, as part of bipolar depression, or concomitant manic symptoms during "mixed states"). ECT should be strongly considered, especially when associated with one of the following features
            a. Acute suicidality with high risk of acting out suicidal thoughts.
            b. Psychotic features.
            c. Rapidly deteriorating physical status due to complications from the depression, such as poor oral intake
            d. History of poor response to medications.
            e. History of good response to ECT.
            f. Patient preference.
            g. Risks of standard antidepressant treatment outweigh the risks of ECT, particularly in medically frail or elderly patients.
            h. Catatonia.
         2. Mania**:** ECT should be particularly considered if
            a. Any of the above features is present.
            b. In the presence of extreme and sustained agitation
            c. In the presence of "manic delirium."
         3. Schizophrenia: According to the APA guidelines, the following associated features predict a favourable response to ECT
            a. Positive symptoms with abrupt or recent onset.
            b. Catatonia.
            c. History of good response to ECT.

ii. Secondary Indications for Use
    1. Catatonia (unrelated to the primary conditions described above). There should be a thorough medical and neurological work-up to identify reversible physical conditions in order to evaluate the risk for ECT and to initiate prompt medical treatment.
    2. Parkinson's Disease: The motoric symptoms can improve, especially with associated "on-off " phenomenon. However, if an acute course of ECT is initiated, provisions should be considered for maintenance ECT in order to sustain a remission.15,16 The attending physician should consider adjusting doses of anti-Parkinsonian agents during the course of ECT due to the possibility of treatment-emergent dyskinesia or psychosis.
    3. Neuroleptic Malignant Syndrome: Antipsychotics should be discontinued and autonomic stability achieved1 before initiating ECT.
    4. Delirium: This should only be rarely considered for patients who require urgent treatment, after medical treatment has been initiated to target the specific cause.1 For those who become delirious secondary to profound physical deterioration (e.g., dehydration) related to the underlying psychiatric disorder (e.g., depression), reversible physical factors should be corrected as quickly as possible before ECT to lessen risk, but the concomitant persistence of delirium should not necessarily impede the consideration of urgent ECT.
    5. Intractable Seizure Disorder Paradoxically, ECT can be considered when treating status epilepticus that is unresponsive to conventional treatments.
    6. Mood Disorder Secondary to Physical Conditions: Reversible underlying physical conditions should be adequately addressed first, in order to speed resolution of symptoms and lessen ECT risks.

iii. Other Conditions
    1. There are insufficient data to advocate the use of ECT for such conditions as primary anxiety disorders, including post-traumatic stress disorder, or primary delusional disorder. Those with chronic pain, along with concurrent affective symptoms, may experience an analgesic effect, but this area requires further study. Studies indicate that those with a personality disorder, particularly borderline type, can benefit if they have a concomitant Axis I mood disorder, but

there is likely a reduced response rate overall, and a higher risk for relapse within one year. Drug-induced extrapyramidal symptoms have also been reported to improve transiently with ECT, but its role in this condition has not been firmly established.

b. According to the APA Guidelines,13 after a successful index course of ECT, continuation of ECT should be considered when
    i. Pharmacotherapy has been ineffective or unsafe in preventing relapse or recurrence.
    ii. The patient (or substitute decision-maker) prefers to continue with ECT, and is willing to comply with the overall treatment plan, including behavioural restrictions associated with outpatient ECT.

4) Aetna 2013

a. Aetna considers electroconvulsive therapy (ECT) medically necessary for members diagnosed with any of the following conditions.
    i. Catatonia, *or*
    ii. Certain acute schizophrenic exacerbations, *or*
    iii. Major depression (unipolar, bipolar, or mixed episode), *or*
    iv. Mania.
    v. Note: More than 20 sessions of ECT in a treatment series is rarely medically necessary.

b. Aetna considers ECT experimental and investigational for the treatment of the following interventions because its effectiveness for these indications has not been established (not an all inclusive list):
    i. Body dysmorphic disorder
    ii. Complex regional pain syndrome
    iii. Dementia-associated agitation and aggression
    iv. Obsessive-compulsive disorder
    v. Post-traumatic stress disorder.

Expert input

George Keepers, MD, OHSU Psychiatry

1) In addition to the conditions noted [depression and bipolar disorder], there is evidence for the efficacy of ECT in treatment resistant schizoaffective disorder and schizophrenia. Even the NICE report acknowledges this. We have frequent referrals for this indication from Oregon State Hospital. Additionally, ECT is a last ditch treatment for some general medical conditions
2) ECT should be considered as first line treatment prior to trials of antidepressants in certain circumstances. ECT is the most effective treatment for depression and the time to achieve response is less than

with pharmacologic treatment. Additionally, ECT is sometimes safer than treatment with medications. For these reasons, it is recommended as a primary treatment in the following circumstances: severe suicidality or homocidality, severe general medical illness, pregnancy. (see The Practice of ElectroConvulsive Therapy: A Task Force Report of the American Psychiatric Association, 2nd edition, section 2.2.1)

3) I have read the NICE report in its entirety. Unlike the Task Force Report or the Cochrane Reviews (which are underway and not completed), the NICE report gives no references and does not clearly explain the methodology used. Part of the process appears to have been to take oral testimony from proponents and opponents of ECT. In any case, this report from the NHS of the United Kingdom gets many of the facts wrong and should not serve as a basis for Oregon policy.
4) ECT should be a first line treatment in these conditions [severe depressive illness, catatonia, prolonged or severe manic episode]. Failure to treat a patient with prolonged severe depression who is malnourished, a patient with catatonia, or a patient with fulminant mania withholds a life-saving treatment that is recognized as a national standard of care. Withholding treatment in these circumstances is malpractice. A physician in an administrative role who refuses to authorize treatment in these circumstances is acting unethically.
5) The risk of death during ECT is estimated from national data as about (.00125%) 1/80,000 treatments. This is considerably lower than the risk of anesthetic death in general which is on the low end .011% or 11 deaths/100,000 anesthesias.
6) This is incorrect [treatment should be stopped when a response has been achieved]. If the treatment is stopped before the patient has had an adequate response, relapse is much more likely
7) This is incorrect [the long term benefits and risks of ECT have not been clearly established]. Continuation and maintenance therapy with ECT are recommended for patients with a history of recurrence and in those for whom treatment with antidepressants has not been effective. There is substantial evidence in the literature that supports this view. See the Task Force Report Section 13.3 as well as the cited papers.
8) I do not agree with this recommendation [HERC staff recommended guideline change from the May 2014 VBBS meeting] which is inconsistent with published national guidelines, the medical literature and the opinions of experts.

Electroconvulsive therapy (ECT)

HERC staff recommendation:

1) Modify GN102 as shown below to specify that vagal nerve stimulation is not paired with depression (but remains on two other lines for specific nerve injury)
    a. Alternate: add notation to "treatments reviewed but not covered" list
2) Add CPT 90870 to line 26 SCHIZOPHRENIC DISORDERS
3) Create a new guideline for ECT as shown below
    a. Include on lines 7 MAJOR DEPRESSION, 26 SCHIZOPHRENIC DISORDERS, 29 BIPOLAR DISORDERS,

GUIDELINE NOTE 102, NON-PHARMACOLOGIC INTERVENTIONS FOR TREATMENT-RESISTANT DEPRESSION

Line 7

Repetitive transcranial magnetic stimulation (CPT 90867-90868) ~~and electroconvulsive therapy (CPT 90870) are~~ is covered only after failure of at least two antidepressants. Vagal nerve stimulation (CPT 64568) is not included on line 7 for treatment of depression.

GUIDELINE NOTE XXX, ELECTROCONVULSIVE THERAPY (ECT)

Line 7,26,29

Electroconvulsive therapy (ECT; CPT 90870) is included on these lines for the treatment of major depression, mania, or schizophrenia when one or more of the following conditions are present:

1) Acute suicidality with high risk of acting out suicidal thoughts.
2) Psychotic features
3) Rapidly deteriorating physical status due to complications from the depression, such as poor oral intake
4) Catatonia
5) History of poor response to multiple adequate trails of medications and/or combination treatments, or the patient is unable or unwilling to comply with or tolerate side effects of available medications, or has a co-morbid medical condition that prevents the use of available medications
6) History of good response to ECT during an earlier episode of the illness
7) The patient is pregnant and has severe mania or depression, and the risks of providing no treatment outweigh the risks of providing ECT.

The frequency and number of treatments need to be determined by the severity of illness and by the relative benefits and risks of ECT treatment. During the course of ECT, it is important to monitor therapeutic responses and adverse effects of treatment. Continuation treatment of patients who have responded to ECT consists of treatment with antidepressant medications and/or a tapering schedule of ECT treatments. Continuation treatment reduces the risk of relapse and should be offered to all patients who respond to ECT. Continuation ECT

treatments should be tapered and discontinued as the patient's clinical condition allows. Maintenance treatment with ECT is indicated to prevent recurrence of depression in patients whose remission of symptoms cannot be maintained with pharmacologic antidepressant treatment.

Electroconvulsive therapy for schizophrenia (Review)

Tharyan P, Adams CE

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 4

http://www.thecochranelibrary.com

[Intervention Review]

Electroconvulsive therapy for schizophrenia

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Editorial group: Cochrane Schizophrenia Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2009.
Review content assessed as up-to-date: 15 February 2005.

Citation: Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD000076. DOI: 10.1002/14651858.CD000076.pub2.

ABSTRACT

Background

Electroconvulsive therapy (ECT) involves the induction of a seizure for therapeutic purposes by the administration of a variable frequency electrical stimulus shock via electrodes applied to the scalp. The effects of its use in people with schizophrenia are unclear.

Objectives

To determine whether electroconvulsive therapy (ECT) results in clinically meaningful benefit with regard to global improvement, hospitalisation, changes in mental state, behaviour and functioning for people with schizophrenia, and to determine whether variations in the practical administration of ECT influences outcome.

Search strategy

We undertook electronic searches of Biological Abstracts (1982-1996), EMBASE (1980-1996), MEDLINE (1966-2004), PsycLIT (1974-1996),SCISEARCH (1996) and the Cochrane Schizophrenia Group's Register (July 2004). We also inspected the references of all identified studies and contacted relevant authors.

Selection criteria

We included all randomised controlled clinical trials that compared ECT with placebo, 'sham ECT', non-pharmacological interventions and antipsychotics and different schedules and methods of administration of ECT for people with schizophrenia, schizoaffective disorder or chronic mental disorder.

Data collection and analysis

Working independently, we selected and critically appraised studies, extracted data and analysed on an intention-to-treat basis. Where possible and appropriate we calculated risk ratios (RR) and their 95% confidence intervals (CI) with the number needed to treat (NNT). For continuous data Weighted Mean Differences (WMD) were calculated. We presented scale data for only those tools that had attained pre-specified levels of quality. We also undertook tests for heterogeneity and publication bias.

Main results

This review includes 26 trials with 50 reports. When ECT is compared with placebo or sham ECT, more people improved in the real ECT group (n=392, 10 RCTs, RR 0.76 random CI 0.59 to 0.98, NNT 6 CI 4 to 12) and though data were heterogeneous (chi-square 17.49 df=9 P=0.04), its impact on variability of data was not substantial (I-squared 48.5%). There was a suggestion that ECT resulted in less relapses in the short term than sham ECT (n=47, 2 RCTs, RR fixed 0.26 CI 0.03 to 2.2), and a greater likelihood of being discharged from hospital (n=98, 1 RCT, RR fixed 0.59, CI 0.34 to 1.01). There is no evidence that this early advantage for ECT is maintained over the medium to long term. People treated with ECT did not drop out of treatment earlier than those treated with sham ECT (n=495, 14 RCTs, RR fixed 0.71 CI 0.33 to 1.52, I-squared 0%). Very limited data indicated that visual memory might decline after ECT compared with sham ECT (n=24, 1 RCT, WMD -14.0 CI -23 to -5); the results of verbal memory tests were equivocal.

When ECT is directly compared with antipsychotic drug treatments (total n=443, 10 RCTs) results favour the medication group (n= 175, 3 RCTs, RR fixed 'not improved at the end of ECT course' 2.18 CI 1.31 to 3.63). Limited evidence suggests that ECT combined with antipsychotic drugs results in greater improvement in mental state (n= 40, 1 RCT, WMD, Brief Psychiatric Rating Scale -3.9 CI - 2.28 to -5.52) than with antipsychotic drugs alone. One small study suggested more memory impairment after a course of ECT combined with antipsychotics than with antipsychotics alone (n=20, MD serial numbers and picture recall -4.90 CI -0.78 to -9.02), though this proved transient. When continuation ECT was added to antipsychotic drugs, the combination was superior to the use of antipsychotics alone (n=30, WMD Global Assessment of Functioning 19.06 CI 9.65 to 28.47), or CECT alone (n=30, WMD -20.30 CI -11.48 to -29.12).

Unilateral and bilateral ECT were equally effective in terms of global improvement (n=78, 2 RCTs, RR fixed 'not improved at end of course of ECT' 0.79 CI 0.45 to 1.39). One trial showed a significant advantage for 20 treatments over 12 treatments for numbers globally improved at the end of the ECT course (n=43, RR fixed 2.53 CI 1.13 to 5.66).

Authors' conclusions

The evidence in this review suggests that ECT, combined with treatment with antipsychotic drugs, may be considered an option for people with schizophrenia, particularly when rapid global improvement and reduction of symptoms is desired. This is also the case for those with schizophrenia who show limited response to medication alone. Even though this initial beneficial effect may not last beyond the short term, there is no clear evidence to refute its use for people with schizophrenia. The research base for the use of ECT in people with schizophrenia continues to expand, but even after more than five decades of clinical use, there remain many unanswered questions regarding its role in the management of people with schizophrenia.

PLAIN LANGUAGE SUMMARY

Electroconvulsive therapy for schizophrenia

The induction of a seizure (fit) for therapeutic purposes by the administration of an electrical stimulus (electroconvulsive therapy or ECT) remains a common treatment option for people with schizophrenia. This review pools data from 26 studies that included over 798 participants in receipt of this treatment. The evidence suggests that courses of ECT can, in the short term, result in an increase in global improvement for some people with schizophrenia.

BACKGROUND

Electroconvulsive therapy (ECT) involves the induction of a seizure (fit) for therapeutic purposes by the administration of a variable frequency electrical stimulus (shock) to the brain via electrodes applied to the scalp. The procedure is usually modified by the use of short acting anaesthetics and muscle relaxants. The former reduces apprehension and the latter avoids unwanted adverse side events such as fractures of the spine or extremities due to the vigorous muscular convulsions that occur if a muscle relaxant is not used. In parts of the world where anaesthetics are not readily available, ECT is still administered without muscle relaxants and anaesthetic agents as unmodified or direct ECT (Andrade 1993).

Electroconvulsive Therapy Review Guidelines

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Electroconvulsive Therapy Review Guidelines

The following guidelines are intended for use by provider hospitals/facilities (general and private) for the development, revision and review of electroconvulsive therapy (ECT) practices. These guidelines are designed to identify critical areas regarding ECT administration and are based on the American Psychiatric Association's recommendations presented in the second edition of *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging* (2001). These guidelines are also intended to assist providers in developing key aspects of their ECT policies and procedures manual. Since these guidelines are not intended to be all inclusive, the APA's *Practice of Electroconvulsive Therapy* should be referred to when a specific subject or topic is under review or in question. APA page numbers are referenced throughout the guidelines to assist in locating information on a particular subject.

The Office of Mental Health staff will use these guidelines in review of ECT practices. These guidelines are not intended to establish regulatory standards for the administration of ECT. Failure to address or adhere to any provision in the guidelines will not necessarily result in regulatory citations, agency actions, or other sanctions. OMH's expectation is that these guidelines will foster the delivery of high quality ECT services.

1. **Use of Electroconvulsive Therapy** (back to top)
    1. The decision to administer ECT is based on an evaluation of the risks and benefits for the individual patient and involves a combination of factors, including psychiatric diagnosis, type and severity of symptoms, prior treatment history and response, identification of possible alternative treatment options, and consumer preference. (APA pp. 5-7)

       Guidelines: Providers should identify how and who determines whether to use ECT as a primary or secondary treatment.

       ECT may be considered as a *primary treatment (or first-line treatment)* for persons exhibiting syndromes such as: severe major depression, acute mania, mood disorders with psychotic features, and catatonia. A decision to use ECT as the primary therapy should be based on an evaluation of the nature and the severity of acute symptoms in conjunction with an evaluation of risks and benefits. ECT may be the initial treatment of choice when a rapid or a higher probability of response is necessary. ECT may also be considered as a primary treatment when there is a history of good response to ECT treatment and/or poor response to alternate treatments during prior episodes.

       ECT is most often used as a *secondary treatment* when a patient has shown insufficient improvement with prescribed treatment(s), which usually includes pharmacotherapy. In addition to lack of substantial clinical response, other reasons to use ECT include, intolerance to side effects of medication or other treatments, deterioration in condition, or appearance of suicidality or pronounced lethargy. In the context of referral for ECT, patients who have not responded to psychotherapy alone should not be considered as having a treatment resistant mental illness - regardless of diagnosis.

    2. ECT is generally used to treat several *principal diagnostic indications* including major depression, mania, and schizophrenia and may be used for *other diagnostic indications* including psychiatric syndromes associated with medical conditions and medical disorders. (APA pp. 8-22)

       Guidelines: Providers should identify principal diagnostic indications and other diagnostic indications for the use of ECT. When identifying persons for possible ECT, a current psychiatric evaluation and diagnosis should be part of the required procedures. Even when no mental illness is diagnosed, other diagnostic indications may include medical disorders such as: Parkinson's disease, intractable seizure disorder and neuroleptic malignant syndrome.

    3. ECT can be administered to persons with severe medical conditions. Although some medical conditions may alter the risk of treatment, there are no "absolute" medical contraindications to the use of ECT. In some medically ill patients ECT may be preferred because of its efficacy and safety profile. (APA pp. 27-29)

       Guidelines: Providers should assure review of medical conditions that may substantially increase risk during the delivery of ECT. A medical history and physical examination are essential before prescribing of ECT to determine risk factors and minimize risks. Factors that significantly increase risk may include: unstable or severe cardiovascular conditions, aneurysm or vascular malformation, increased intracranial pressure, cerebral infarction, pulmonary insufficiency and a patient medical status rated as ASA level 4 or 5. This list is not all-inclusive, and ECT providers should be familiar with the range of medical conditions that may enhance risks. Approaches to minimizing risks may include modifications in patient management, changes in patient preparation or adjustments in treatment delivery technique.

    4. The decision to administer ECT to special populations of patients should include an appraisal of specific risks and benefits for the individual patient. It should also address the type, likelihood, and potential persistence of adverse effects as well as the possible impact of ECT on the patient's medical status and current medical treatments. Special populations identified by the APA include:

Coexisting medical illnesses (e.g. neurologic and cardiovascular disorders) and their treatment may affect both the likelihood of response and the risks of ECT. It is critical to recognize potential interactions among coexisting medical conditions, physiologic events associated with anesthesia, electrical stimulation, and induced seizure activity when proposing and administering ECT.

Elderly patients may receive ECT regardless of age. The efficacy of treatment does not diminish with advancing age. ECT may have a lower risk of complications than some forms of pharmacotherapy in the elderly.

Pregnant women and nursing mothers may receive ECT during all trimesters of pregnancy, puerperium and nursing. ECT may be less risky than alternate pharmacologic treatment or non-treatment of mental illness during pregnancy.

Children and Adolescents should receive ECT only when it is evident that other viable treatments have been ineffective or if other treatments cannot be administered safely. (APA pp. 31-52)

Guidelines: Providers should address special populations of patients who may receive ECT treatment. OMH recognizes that hospitals/facilities may provide ECT services to other special populations (e.g. mental retardation/developmental disabilities) in addition to the ones specifically identified by the APA. Facilities providing ECT to a special population should develop policies reflecting specific treatment considerations for those groups of individuals.

Providers should require an evaluation of a patient's condition prior to ECT to determine whether they should be considered as a member of a special population. For patients who are identified as belonging to a special population, a tailored risk/benefit assessment should be completed by appropriate medical professionals. Pregnant patients should receive an obstetric consultation prior to ECT. Nursing mothers should be informed of the effect medications may have on breast milk and what steps may be taken to decrease infant exposure. It is recommended that for children under the age of 13, concurrence by two consultants, at least one being independent, who are experienced in the treatment of children be obtained before ECT is administered .

Any modifications to the standard ECT treatment regimen must be clinically documented at the time of ECT. For example, persons with substantial symptoms of neurologic disorders (e.g. NMS) or persons at risk of hyperkalemia may require nondepolarizing muscle relaxants instead of succinylcholine and persons with porphyria should receive a nonbarbiturate anesthetic.

Policies and Procedures: Policies and procedures should describe how ECT will be used in treatment; assure assessment of medical risk and current psychiatric evaluation; and identify treatment considerations for special populations generally served by the provider.

2. **Staffing** (back to top)
    1. At each facility offering ECT, a psychiatrist privileged to administer ECT should be designated as having the responsibility for developing, updating and overseeing compliance with policies and procedures for ECT, including issues related to staffing, equipment, and supplies. (APA pg. 109)

    Guidelines: Providers should designate a psychiatrist as the coordinator of ECT services. The coordinator of ECT services should be a psychiatrist privileged to administer ECT and should have clearly defined duties and responsibilities.

    2. An ECT treatment team should be appropriately trained and consist of at least an ECT privileged psychiatrist, an anesthesia provider, and a recovery nurse. In addition, an ECT treatment nurse or assistant in the treatment room is recommended. Treatment facilities should ensure that the ECT psychiatrist is privileged by the facility to perform ECT. (APA pp. 109-112, 241-243)

    Guidelines: Providers should identify the composition of the ECT treatment team and should include minimum staffing requirements. The use of the term "team" does not imply that staff members have to be

identified by name. Instead the designation of "team" members should be identified by functional titles (e.g. ECT Nurse (RN)),since it is understood some flexibility in staffing may be necessary. Although team members may not always be the same staff, it is expected that all staff providing ECT will be properly trained in their disciplines to provide ECT. Since there are no national standards regarding training, qualifications and privileging, each treatment facility should indicate required training and qualifications of all members. Providers should describe the process used to privilege physicians administering ECT.

Anesthesia providers should be, at minimum, privileged to deliver general anesthesia and may include anesthesiologists or nurse anesthetists. If a nurse anesthetist is used to provide anesthesia, the treatment facility should establish policies and procedures assuring the timely on-site availability of an anesthesiologist as required under NYCRR Title 10 Part 405.13. Patients identified as high risk should only be treated by a qualified anesthesiologist who is experienced in ECT procedures. Policies and procedures should clearly identify the process used to determine high-risk patients. The Office of Mental Health recommends that free standing facilities (e.g. Article 31 private psychiatric hospitals, Article 28 licensed diagnostic and treatment centers) only use certified anesthesiologists.

Since the Office of Mental Health advocates that the ECT psychiatrist not administer both anesthesia and ECT, the facility should develop an ECT administration plan which clearly describes the process. The plan should be sent to OMH's Chief Medical Officer for review and approval.

3. Responsibilities of the ECT treatment team should be detailed in the ECT policy and procedure manual. (APA pp. 113-115).

Guidelines: Each facility is responsible for designating required tasks to the appropriately qualified staff. These responsibilities should be clearly defined in the policy and procedure manual. It is suggested that specific responsibilities be designated to treatment team members as follows:

ECT Psychiatrist - As the treatment team member with the most comprehensive experience and training in ECT, the ECT psychiatrist should maintain overall responsibility for the administration of the treatment. The ECT psychiatrist's responsibilities include: 1) assessing the patient before beginning ECT, 2) ensuring that all pre-ECT evaluations have been completed, 3) determining that ECT is still indicated, 4) ensuring that ECT is delivered in accordance with policies and procedures, 5) instituting modifications in ECT as indicated, and 6) ensuring proper documentation of evaluations and treatment results.

Anesthesia Provider - Responsibilities generally include: 1) managing the airway, 2) administering ultra-brief anesthetic and relaxant agents, 3) monitoring cardiopulmonary functioning, and 4) managing acute adverse events.

Recovery Nurse - This person is a registered nurse whose responsibilities include monitoring of vital signs, pulse oximetry, ECG, and mental status, 2) administering oxygen and intravenous fluids, 3) provision of suctioning, and 4) management of postictal disorientation and agitation.

ECT Nurse or Assistant - This person is usually an RN but may be an LPN or an assistant with ECT training and experience. Responsibilities should be consistent with training and clinical competence and generally include assisting the ECT psychiatrist and the anesthesia provider with duties such as: 1) coordinating treatment logistics, 2) readying the treatment area for ECT, including checking the proper functioning of equipment (e.g. suction, physiological monitoring equipment, etc.), 3) assisting patients to and from treatment area, 4) applying stimulus and monitoring electrodes, and monitoring vital signs. Additional duties for ambulatory ECT patients may include assessing patients before each ECT treatment and delivering post recovery care.

Policies and Procedures: Policies and procedures should identify the duties and qualifications of the psychiatrist designated as coordinator of ECT services; and identify staff members by functional title who will constitute an ECT treatment team and delineate staff responsibilities. When an anesthesiologist is not routinely included on the ECT treatment team, policies and procedures should provide for the availability of an anesthesiologist on-site at the facility and for including an anesthesiologist on the team during treatment

of high risk patients.

3. **Treatment Site and Equipment** (back to top)
   1. The treatment site should be conducive to the delivery of ECT treatment for both the patient and staff. (APA pg. 117)

      Guidelines: The treatment site should include separate areas for waiting, treatment, and recovery. If outpatient ECT treatment is provided, there should also be space identified for patients and those accompanying the patient during the post recovery period. Policies should identify where ECT related equipment and supplies are stored within the treatment site. Staff responsibilities regarding the treatment site should be included in the policy and procedure manual. Patient medical records should be readily accessible to the ECT treatment team during treatment.

      Since ECT differs from other "typical" operative procedures, hospitals who designate general operating rooms, surgical suites, and/or common recovery rooms for ECT treatment should identify any additional equipment that is specific to the delivery of ECT and should be available during treatment. When such treatment sites are used, providers should delineate any additional steps that may be needed to assure patient privacy. In this section, as well as in sections 3.b, 3.c and 3.d, providers may reference existing practices for these treatment sites, but should also specifically address aspects unique to ECT.

   2. The treatment site should contain sufficient quantities of required and optional equipment, medications and supplies to administer ECT safely. (APA pg. 118)

      Guidelines: Providers should identify the equipment to be available in administering ECT. Equipment should be available in both the ECT treatment area and the recovery area to provide suction; deliver intermittent positive-pressure oxygen; monitor vital signs, including cardiac rhythm and hemoglobin oxygen saturation. The treatment area should also contain equipment for intubation, seizure induction (brief pulse waveform ECT device), physiologic monitoring including EEG, and resuscitation. The recovery area should also contain ECG monitoring and pulse oximetry devices. More specifically, standard equipment in the treatment area includes: 1) stretcher or bed with side rails and the capacity to raise both the head and feet, 2) automatic or manual blood pressure monitoring device, 3) stethoscope, 4) ECT device with built-in EEG monitoring, 5) ECG monitoring equipment, 6) sphygmomanometer cuff to permit detection of ictal motor duration, 7) pulse oximeter, 8) oxygen delivery system, 8) suction apparatus, 9) intubation set for managing airways, and 10) reflex hammer. When treating patients who are at significantly increased risk of musculoskeletal injury (e.g. severe osteoporosis) or when using nondepolarizing muscle relaxant agents (e.g. curare, atracurium, mivacurium, rocuronium), it is recommended that a peripheral nerve stimulator be available to ensure the adequacy of muscle blockade before delivering the electrical stimulus. A defibrillator should be readily available. Access to a backup ECT device and additional cables is suggested; however, because of cost, this may not be reasonable in smaller hospitals/facilities. Staff responsibilities relating to equipment should be delineated including its availability in the treatment area, safety checks and general care and maintenance.

   3. Medications used during the administration of ECT should be located within the treatment site. (APA pp. 118-119, 122-123)

      Guidelines: Pharmacologic agents that may be required during ECT treatment should be identified. Such medications include: 1) primary anesthetic agent, 2) primary muscle relaxant, 3) an anticholinergic agent, 4) medications for first-line management of arrhythmias, hyper- or hypotension, and cardiac arrest, 5) medications for the initial management of severe bronchospasm or anaphylactic shock, other agents for managing status epilepticus, 6) antinausea medications, and 7) non-narcotic analgesics. Practices should cover storage and staff access to medications within the ECT treatment area, including maintaining a current inventory of controlled drugs. NOTE: APA's Recommendations for ECT practice also suggests additional medications that facilities may choose to have available (APA pp. 122 and 123).

   4. Sufficient medical supplies should be available in the ECT treatment area. (APA pp. 119-120, 123-124)

Guidelines: Providers should assure availability of supplies needed in the ECT treatment area to induce anesthesia, monitor physiologic functions, and provide ventilation and resuscitation. Staff responsibilities for ordering and assuring the availability of required supplies should be identified. NOTE: An extensive list of necessary and suggested supplies can be found in the APA recommendations (APA pp. 123 - 124) .

Policies and Procedures: Policies and procedures should ensure availability of an appropriately equipped and functional treatment site conducive to providing ECT, including provisions for equipment, medications, and medical supplies.

4. **Informed Consent** (back to top)
    1. Patients have the right to be fully informed about the proposed ECT treatment. Unless they lack capacity, patients have the right to consent to ECT treatment or to refuse treatment. If a patient determined to have capacity refuses ECT treatment, ECT treatment would not be sought through court authorization; court authorization would be sought only in cases where the patient is determined to lack capacity. Decisions regarding the administration of ECT should be made in a collaborative manner between the patient and physician. (APA pp. 97-98)

    Guidelines: Providers should address the process used to obtain informed consent. NYS Law Section 33.03 (b)(4) mandates that facilities obtain patient consent for ECT. Based on NYS regulations (NYCRR Parts 527. 8 and 27.9), the informed consent process should include: 1) the provision of adequate and understandable information of the ECT procedure including: reason for treatment, expected benefits, reasonably foreseeable risks, and any reasonable alternatives available 2) an evaluation of the patient's capacity to factually and rationally understand and appreciate the nature and consequences of the proposed treatment and their ability to reach reasonable decisions based on such information, 3) evidence that the patient was made aware that they have a right to have a person of his or her choice present when consent is sought 4) evidence that the patient was informed that they have a right to refuse treatment and were informed of the possible consequences of such refusal.

    2. Prior to ECT treatment, informed consent for ECT must be obtained from the patient (18 years and older) or if the patient is under 18 years, from the parents or the legal guardian, except when it has been determined that the patient lacks capacity to consent. (APA pp. 98-100)

    Guidelines: Providers should address the process to obtain informed consent, including procedures to follow when it is not clear whether the patient has sufficient capacity to give consent (e.g. use of an independent consultant). Circumstances under which informed consent is required includes, at minimum: before initial acute treatment, when additional treatments are required beyond the number originally proposed, and before beginning continuation or maintenance ECT. Informed consent should be obtained by the patient's attending physician, treating psychiatrist, or another physician who is knowledgeable about the patient and about ECT treatment procedures. To limit risks to patients and to ensure continuity care, OMH recommends that consent be obtained directly by a physician responsible for the care and treatment of the patient. Some hospitals may require separate consent for ECT anesthesia. If so, this consent should be obtained by the designated anesthesia provider.

    3. Information describing ECT should be conveyed to the patient in a consent document that can be easily understood by the patient. Copies of documents should be provided to the patient. In areas where facilities serve large numbers of people who speak a language other than English, whenever possible documents should be written in the primary language of the patient. This is not to imply that consent forms have to be available in every conceivable language. Each facility should evaluate their need for consent forms in languages other than English.(APA pp. 100-102)

    Guidelines: Providers should ensure that patients sign a written consent document and should include specific information provided to the consentor, including but not limited to: 1) reason for the recommendation of ECT, 2) description of alternative treatments, 3) description of ECT procedure, 4) discussion of the benefits and risks of the different stimulus electrode placements and the rationale for the electrode placement being recommended, 5) range of the number of treatments the consentor is approving, 6) statement that there is no guarantee that ECT will be effective, 7) statement regarding the need for

continuation/maintenance somatic treatment, 8) description of major risks and their likelihood of occurrence, 9) description of common side effects, 10) statement that consent for ECT also includes consent for clinically necessary emergency treatment, 11) description of restrictions on patient behavior before, during, and after treatment, 12) evidence of an opportunity for patient to ask questions, 13) statement that ECT is voluntary and may be withdrawn by the patient at any time.

OMH supports the practice of obtaining input from treatment team members, family members and patient identified friends, when appropriate, during the consent process.

If English is not the patient's primary language, the facility should ensure that a translator is available to convey the specific information that is part of the consent process.

4. The capacity to provide voluntary consent for ECT should be determined by the attending psychiatrist. Unless evidence to the contrary is compelling and it has been determined by a court, individuals with mental illness are considered to have capacity to consent to ECT. The medical record should include documentation of the consent process, including the determination of capacity and the discussion of any heightened risks or necessary treatment modifications. (APA pp. 102-104)

Guidelines: Providers should ensure that a patient is evaluated to determine their capacity to give consent. NYS regulations define *capacity* as the patient's ability to factually and rationally understand and appreciate the nature and consequences of proposed treatment, including the benefits, risks and alternatives to the proposed treatment, and to thereby make a reasoned decision about undergoing the proposed treatment. Article 28 facilities should also refer to the Department of Health requirements under NYCRR Title 10 Part 405. A patient is not considered to be lacking in capacity based solely on their refusal of ECT treatment. When a patient is deemed as lacking capacity, requirements for obtaining consent for treatment should adhere to NY State laws and regulations as noted under Parts 27.9 and 527.8.

Policies and Procedures: Policies and procedures should address the process used to obtain informed consent from patients (both from adults and from parents/legal guardians for patients under 18 years old), including evaluation of capacity; the written consent document to be used; and provisions to address non-English speaking populations.

5. **Pre-ECT Evaluation** (back to top)
   1. Specific components of the evaluation of patients identified for ECT vary on a case-by-case basis; however, each facility should identify a minimal set of evaluations to be undertaken in all cases. The ECT evaluation should be performed by an individual privileged to administer ECT as well as by the anesthesia provider. Laboratory testing is used to confirm the presence and severity of medical risk factors. No specific laboratory tests are routinely required as part of the pre-ECT work up. (APA pp. 77-79)

   Guidelines: Evaluation prior to ECT should include a discussion of common indications for additional tests and consultations. An individual privileged to administer ECT should review the pre-ECT evaluation ensuring that:

   1) psychiatric history and functioning were evaluated, 2) the medical status of patient was reviewed, 3) an anesthetic evaluation was completed, 4) laboratory results and radiological studies, if any, were reviewed and 5) indicated consultations were obtained and reviewed.

   Along with documenting the above findings in the clinical record, the pre-ECT evaluation notes should summarize the indications for ECT as well as the anticipated benefits and risks of ECT. If indicated, it should also suggest any additional evaluative procedures, alterations to ongoing medications (including the prescribing of medications that augment ECT), or modifications to ECT or anesthetic procedures. More specifically, it is recommended that the pre-ECT evaluation include:

   1) psychiatric history, including past response to ECT, 2) mental status examination, including a cognitive examination 3) general medical history and examination to identify medical risks of ECT focusing on neurologic, cardiovascular, pulmonary systems, and effects of previous anesthesia inductions, 4) review of

all medications taken by the patient including prescribed and over-the-counter medications, 5) assessment of dental status and an inspection of the mouth in order to identify dental problems, loose or missing teeth, or the presence of dentures or other appliances, 6) a minimum battery of laboratory tests (obtaining a complete blood count, serum potassium and sodium levels, and an electrocardiogram (ECG) is recommended practice, but not mandatory), 7) additional tests identified during preliminary evaluations, 8) an anesthetic evaluation, addressing risks and specifying any necessary modifications in ongoing medications or standard anesthetic technique.

After completing the pre-ECT evaluation, the ECT psychiatrist should clearly document any special considerations or indicate any necessary modifications to standard ECT procedure and write pre-procedure orders related to the administration of ECT.

2. ECT may be provided on an inpatient or outpatient basis. During the pre-ECT evaluation the treating physician should determine whether ECT is appropriate on an inpatient or outpatient setting or a combination thereof. Certain situations will indicate a switch from inpatient to outpatient setting and visa-versa. (APA pp. 125-127)

Guidelines: Providers should identify criteria used to determine the appropriate setting for the delivery of ECT treatment. Patient preference should be taken into consideration when making determining the best setting for the delivery of ECT.

Inpatient setting would be appropriate if:
1) patient's psychiatric condition precluded safe and effective management on an outpatient basis (e.g. high risk of suicide), 2) patient exhibited psychotic ideation, severepreexisting cognitive impairment, or extreme inanition, 3) patient was at high risk of serious medical complications or has anticipated risks that may be difficult to detect or manage, 4) patient was unwilling or incapable of complying with required outpatient protocols (e.g. NPO order), 5) patient did not have availability of a caretaker during the treatment period

Outpatient setting would be appropriate if:
1) the type and seriousness of the patient's mental illness did not present significant risk to management of the patient 2) anticipated risks associated with ECT were detectable and manageable both during ECT and at home 3) the treating physician would maintain overall responsibility for the patient during the ECT treatment period 4) one or more caregivers were identified and had agreed to be available throughout the index ECT course to assist with patient safety, including accompanying of the patient to and from treatment, and monitoring compliance with treatment regimen, 5) the patient was capable and willing, with caregiver assistance to follow behavioral requirements

Limitations on patient behavior that must be followed during outpatient ECT treatment include:

1) avoiding activities that are most likely to be substantially impaired by the adverse cognitive effects of ECT including driving during an index treatment course, 2) following prescribed dietary, bowel, bladder, and grooming instructions, 3) complying with specified medication regimens, 4) reporting of any adverse effects and/or apparent changes in medical condition prior to the next treatment.

Policies and Procedures: Policies and procedures should address requirements for pre-ECT evaluations and findings to be documented in the patient's record.

6. **Treatment Procedures** (back to top)
   1. Each ECT team member should have clearly defined roles and responsibilities while preparing to administer ECT. (APA pp. 127-128)

Guidelines: Providers need to clearly identify and define roles and responsibilities of all ECT team members in all aspects of the ECT preparation phase (see sections 2.b. and 2.c.). Although a facility may designate roles and responsibilities differently than noted below, each facility is responsible for ensuring that all required roles and responsibilities are completed by appropriate and qualified staff. Before the first treatment the psychiatrist should check the medical record to ensure that the pre-ECT evaluation and

informed consent are complete. Each team member's role should be covered, including responsibilities such as verification of nothing-by-mouth compliance; patient preparation including removing eye glasses, hearing aids, dentures and jewelry, ensuring hair is clean and dry; recording of vital signs; insertion of mouth guard/bite block; review by the attending physician and anesthetist of the patient's current general medical condition; initiation of intravenous access; administration of prescribed medication; preparation of the ECT area; checking of equipment; preparation of the scalp electrode sites; etc.

2. Airway management during ECT treatment is the responsibility of the anesthesia provider. (APA pp. 129-131)

   Guidelines: The anesthesia provider in airway management should include:

   1) verification that required equipment is properly functioning and that necessary supplies for resuscitation are available, 2) determination of the ability to provide adequate ventilation prior to administration of muscle relaxant, 3) provision of oxygenation using positive pressure ventilation until spontaneous respiration resumes, 4) ensuring protection of teeth and other oral structures, unless otherwise contraindicated 5) ensuring that supplementary oxygen is available in the recovery area.

3. A number of medications are commonly used in conjunction with ECT. The specific medications administered during ECT treatment sessions should be individualized based on the needs of the patients. (APA pp. 131-139)

   Guidelines: Providers should address the use of various medications primarily used to modify ECT response, including anticholinergic agents, anesthetic agents, muscle relaxants, and cardiovascular agents. ECT should be carried out using ultra-brief, light general anesthesia. Unconsciousness should last only several minutes. A skeletal muscle relaxant should be used to modify convulsive motor activity and enhance airway management. Complete paralysis is neither necessary nor desirable.

4. There are a variety of devices available to administer ECT. Although all of these devices must have had FDA approval prior to marketing in the United States , devices may vary in the number and types of features included. (APA pp. 139-150)

   Guidelines: Providers should describe the type of ECT device that the facility uses and should include information about settings, calibration, testing, maintenance and staff responsibilities. ECT staff should be familiar with the device controls and settings. All ECT devices should undergo regular retesting or recalibration by a biomedical technician or otherwise qualified staff, with particular attention paid to electrical safety and calibration of stimulus output. At a minimum, testing should occur on an annual basis; testing intervals should comply with manufacturer's recommendations or local facility requirements, whichever is more frequent.

   Policies should indicate that the device output will be a constant current brief pulse waveform. The regular use of sine wave stimulation in ECT is not supported by OMH . Any use of sine wave stimulation should be by exception only, on a case-by-case basis. The decision to use sine wave stimulation must be justified and documented in the treatment record. Patients should be informed of the risks and anticipated benefits of using sine wave stimulation as compared to brief pulse stimulation and should have the option to choose brief pulse stimulation.

5. Choice of electrode placement is important and should be determined for each patient on an individualized basis prior to ECT treatment. The ECT psychiatrist should be skilled in administering both unilateral and bilateral ECT. (APA pp. 150-158)

   Guidelines: Providers should address the process used to determine electrode placement and positioning. Decisions regarding electrode placement should be made by the ECT psychiatrist in concert with the attending psychiatrist and the patient. The choice of unilateral versus bilateral electrode placement should be based on an ongoing analysis of risks and benefits to the patient. Decisions about electrode placement should be made in concert with decisions about stimulus dosing.

6. The primary goal of stimulus dosing is to produce an adequate seizure (ictal response) with therapeutic properties that also minimize adverse cognitive side effects. (APA pp. 158-161)

   Guidelines: The ECT practitioner should use a recognized method for selecting an individualized stimulus dosage for each patient. The facility's preferred method to individualize electrical stimulus dosing should be indicated.

   Empirical titration methods are used for identifying seizure threshold at the beginning of an ECT course. Many practitioners use an empirical titration procedure because they are able to identify the degree to which subsequent stimulus dosages exceed seizure threshold. Such determinations are particularly important when unilateral electrode placement is used. When using empirical titration, policies should clearly state the maximum number of restimulations permitted during an ECT treatment session; 4 or 5 is the common cutoff point.

   Formula based methods determine stimulus intensity using standardized formulas, which include some individualization. The formulas used vary from simple formulas with single variables (e.g. patient's age) to more complex formulas with multiple variables (e.g. patient age, electrode placement, gender, etc).

   Fixed stimulus is a method to determine dosage in which patients receive a high, fixed dosage of electricity without regard to individual differences. This method is not recommended and should be reserved only for patients with sufficiently serious concomitant medical conditions in which avoiding a subconvulsive stimulation is a priority.

7. During ECT treatment, physiologic monitoring is essential, with key indicators including: motor and EEG seizure monitoring, cardiovascular monitoring, and oximetry (APA pp. 161-167)

   Guidelines: Providers should address patient monitoring during the ECT process.

   Seizure duration should be monitored to ensure that an adequate ictal response occurred, to detect prolonged seizure activity, and to regulate stimulus dosage. Since EEG and motor durations of seizures are not always equivalent, it is recommended that seizure duration be documented by motor ictal duration as well as by EEG.

   EEG monitoring should be carried out on a one-channel basis, at a minimum. The location of EEG monitoring leads should maximize the detection of ictal EEG activity (e.g. frontal-mastoid placement).

   ECG monitoring should begin prior to anesthesia and continue until spontaneous respiration resumes. ECG machines should be capable of producing a paper printout.

   Vital signs including blood pressure and heart rate should be measured and documented before anesthesia and at intervals throughout the procedure, continuing until any ECT related changes have stabilized.

   Oximetry should be carried out throughout the procedure to ensure that oxygenation is adequate.

   Other monitoring may be necessary based on an individual's medical condition and during pregnancy.

8. Management of missed seizures, abortive or brief seizures, and prolonged seizures should be addressed. (APA pp. 167-172)

   Guidelines: Providers should address:

   Missed seizures including procedures for identifying "missed" seizures (subconvulsive administration) and specification of the minimal interval between stimulations (at least 20 seconds) and the maximum number of restimulations permitted (4-5 are usual).

   Abortive or brief seizures including procedures for identifying aborted or brief seizures (typically, less than 15 seconds of ictal motor activity), specifying the length of time before restimulation can occur (usually

longer than 45 seconds), and determining the adequacy of treatment.

Prolonged seizures including procedures for identifying a prolonged seizure (generally > or = 3 minutes) and steps for managing prolonged seizures, including administration of anticonvulsants and monitoring of patients for airway blockage, respiratory depression and/or cardiovascular instability.

9. Physicians administering ECT should assess whether adverse effects are present. If adverse effects are observed, the ECT team should ensure that any indicated interventions occur. This may include immediate management of adverse effects or modifications in treatment technique in subsequent ECT treatments. (APA pp. 59-74)

   Guidelines: Providers should address assessment and treatment of potential adverse effects including:

   Cardiovascular effects: The process of monitoring for adverse cardiovascular effects is outlined in section 6.g and should include the monitoring of vital signs (blood pressure, pulse, and respiration) and the use of electrocardiograms (ECG) and pulse oximetry during ECT treatment and recovery. Providers should delineate staff responsible for managing specific cardiovascular complications typically associated with ECT treatment and identify requisite equipment and supplies. Alternatively, other existing hospital procedures or standard protocols (e.g. ACLS) may be referenced.

   Prolonged seizures: As described in section 6.h, the steps to be taken by staff to terminate prolonged seizures should be identified. This should include a statement about the specific seizure duration at which a seizure would be defined as prolonged (generally > or = 3 minutes).

   Respiratory effects including prolonged apnea: The adequacy of oxygenation should be assessed by pulse oximetry throughout the treatment and recovery period (see section 6.g). The treatment area should contain resources for maintaining an airway for an extended period and for intubating patients if indicated.

   Headache, muscle soreness, and nausea: The recognition of these systemic side effects should be addressed and include symptomatic treatments that may be considered.

   Policies and procedures addressing adverse effects should allow for flexibility and should not supersede clinical judgment but should outline usual procedures in emergency situations.

10. Management of the patient after the delivery of the ECT treatment should be addressed. (APA pp. 172-174)

    Guidelines: Providers should describe:

    Management in the treatment area immediately following the delivery of ECT including identification of staff responsibilities during the recovery and post recovery period. Patients should not be released from the treatment area until spontaneous respiration has resumed, vital signs are sufficiently stable, and no adverse effects are present that would require immediate medical evaluation or intervention. Once patients are medically stable they can be moved to the recovery area.

    Management in the recovery area including assignment of staff duties and management of postictal delirium. Management of the patient while in recovery should be under the supervision of the anesthesia provider. Recovery area nurses should provide continuous observation and supportive care, and should monitor vital signs including heart and respiratory rates, monitor pulse oximetry; and monitor EKG activity when the patient has cardiovascular disease or when dysrhythmias are anticipated or detected. EKG equipment should always be readily accessible in the recovery area. Recovery area staff should immediately alert the anesthesia provider to any situation that potentially requires medical intervention. Procedures should describe the management of postictal delirium and agitation, including supportive interventions and the use of medications, such as intravenous or intramuscular sedatives.

    Post-recovery care including discharge procedures identifying minimum criteria that patients should meet prior to discharge. Post-recovery care is important for patients receiving ECT treatment on an outpatient basis. A space should be identified within the facility for patients and those accompanying the patient during

the pos-recovery period. Patients should be released in the care of a significant other or caregiver. It is inadvisable for patients to drive immediately following ECT treatment. Instructions about other behavioral limitations should be reiterated before the patient is discharged, and the provision of written instructions is strongly suggested. Patient adherence to behavioral limitations and the decision to continue with outpatient ECT should be reassessed on a treatment-by-treatment basis with consideration given to patient preference. However, changes in clinical status, such as the emergence of suicidal intent or psychosis or the lack of a reliable caregiver to transport the patient, may necessitate a switch to inpatient care. (See also section 5.b.)

11. The frequency and number of treatments need to be determined by the severity of illness and by the relative benefits and risks of ECT treatment. (APA pgs, 174-177)

Guidelines: Providers should address the following:

Frequency of treatments, including the usual number of weekly treatments (generally, 3 per week), variations in frequency, and review of frequency, based on patient response. In general, the use of more than one adequate seizure per treatment session is discouraged.

Number of treatments, including the usual number of treatments for specific types psychiatric disorders (e.g. 6-12 treatments for major depression), changes in the course of treatment based upon patient response, treatment modifications based on the severity of adverse effects (e.g. decreasing the number of treatments or suspending ECT), and the requirement for formal assessment of the need for continued ECT. All of these should be discussed with the patient. Repeated courses of treatment are sometimes necessary and should be addressed as part of facility policies and procedures.

Policies and Procedures: Policies and procedures for ECT treatment should address the following: the device to be used to administer ECT and description of its use and its maintenance; airway management; use of medication; policies for stimulus dosing and electrode placement; policies for patient monitoring and seizure management; assessment and treatment of adverse effects; and post-treatment.

7. **Evaluation of Treatment Outcome** (back to top)
   1. During the course of ECT, it is important to monitor therapeutic responses and adverse effects of treatment. (APA pp. 197-202)

      Guidelines: Providers should address requirements for clinical assessments performed by the attending psychiatrist or designee. Assessment should occur prior to ECT and after every one or two treatments, usually within 24 hours after treatment. Formal clinical rating instruments are available and may be employed in documenting therapeutic responses and changes in symptoms. Policies should also discuss the need to determine whether ECT should be continued, reduced in frequency, or suspended when hypo-mania or mania emerges during an ECT course.

      During the course of treatment, monitoring should include the presence and severity of disorientation, anterograde amnesia (by use of objective measures), treatment emergent mania, etc. and should also include patient self-reporting. Assessment of orientation and memory should be completed before the initial ECT treatment and at least weekly throughout the treatment course. If disorientation or memory loss are substantial during treatment, modifications to the ECT procedure (from bilateral to right unilateral electrode placement, decrease in electrical intensity, longer intervals between treatments, altering dosage of medications, etc.) may be warranted.

      Before each scheduled treatment session, evaluations should address other identified adverse effects that may increase risks during treatment. Policies should clearly identify any additional assessments of therapeutic responses or adverse effects that will be used and by whom they will be administered.

      Policies and Procedures: Policies and procedures should address monitoring therapeutic responses and adverse effects of treatment.

8. **Documentation** (back to top)

1. It is the responsibility of the facility's medical director or designated medical staff to ensure that adequate documentation is maintained in the medical record. (APA pp. 217-220)

Guidelines: Providers should identify the documentation as well as any specific documents required in the clinical records. There is no standard form that must be included as part of this documentation process. Forms may contain one or more of the listed elements and documentation may include progress notes rather than a designated form. Staff responsible for completing each type of documentation should be identified.

It is recommended that before beginning treatment the following information be documented :

1) ECT assessment or referral note, including a discussion of anticipated benefits and risks, 2) current mental status, 3) signed consent document, 4) documents covering other elements of informed consent requirements, including assessment of capacity and any special risks, 5) pertinent laboratory results, 6) consultation reports, 7) identification of any substantial alterations to the ECT procedure.

It is recommended that prior to a continuation or maintenance series of ECT the following information be documented:

1) rationale for continuation/maintenance of ECT, 2) updated consent form, 3) documents covering other elements of informed consent requirements, as needed.

It is recommended that before extending continuation/maintenance ECT beyond the original period of treatment, the following information be documented:

1) rationale for ongoing treatment with continuation/maintenance ECT.

It is recommended that during ECT treatment the following information be documented:

1) Treatment notes, entered at least every two treatments, by the attending physician or designee noting therapeutic response and any substantive change. (Presence or absence of adverse cognitive effects should be entered weekly) 2) justification for exceeding a specified maximum number of treatments, as established by the facility policy 3) for continuation /maintenance ECT: documentation of beneficial response prior to each treatment or at least once a month; adverse cognitive effects should be noted at least every three treatments.

It is recommended that during each ECT treatment session the following information be recorded:

1) baseline vital signs, 2) medication given prior to treatment, during treatment, and in the recovery area, 3) anesthetist's note describing patient's condition while in treatment and recovery, 4) when applicable, notes covering any major alterations in risk factors or presence of adverse effects or complications, 5) stimulus electrode placement 6) stimulus parameter settings for each stimulus, 7) seizure duration and/or other measures of seizure adequacy, 8) vital signs during treatment and in the recovery area, 9) occurrence and management of any complications and patient's condition upon leaving the recovery area.

It is recommended that after completion of an ECT course or a continuation/maintenance ECT series the following information should be included in the clinical record: 1) summary of therapeutic outcome and adverse effects, 2) plans for post-ECT clinical management, and for any follow-up to address adverse effects.

Policies and Procedures: Policies and procedures for documentation in the medical records should include requirements for pre-treatment; continuation/maintenance treatments; during treatment sessions; and at the conclusion of a course of ECT treatment.

access the site. Unauthorized attempts to upload information to the site or change information on the site or to interrupt or disrupt operation of the site are strictly prohibited and may subject the perpetrator to both civil and criminal penalties under Federal and/or State law.

Electroconvulsive Therapy (ECT)

Definition:

ECT is a mental health procedure used to treat medically stable individuals with mental illness who are drug resistant for treatment of some psychiatric disorders. Those disorders may include major depression, bipolar disorder, and schizophrenia. The service must be provided in an appropriately equipped facility by a trained and experienced licensed psychiatrist. This service may be delivered as a part of an inpatient hospital per diem as well as delivered as an outpatient procedure in an outpatient surgery environment.

Policy:

ECT mental health services are available to Medicaid Managed Care eligible adult members, age 21 and over.

Licensing:

A hospital license or appropriate license for a surgical center is required to provide this service.

Program Expectations:

This service is provided in an appropriately equipped, safe treatment environment that is staffed with skilled medical personnel to prepare the client for the procedure and assist the client in recovery following the delivery of the procedure. A hospital license or appropriate license for a surgical center is required to provide this service.

Staffing:

Psychiatrists

Advanced Practiced Registered Nurses (APRN)

Nebraska licensed RN's working within their scope of practice

Nebraska licensed anesthetist working within their scope of practice

Length of Service:

As medically necessary based upon the psychiatrist's assessment and client's response to the treatment and according to the treatment plan. Usually provided intermittently for a series which may be twice weekly. Clients at times receive maintenance at a less frequent basis.

Special Procedures

NA

Billing:

Charges are included in the inpatient hospital per diem when the client is admitted to the hospital. The procedure may be billed as an outpatient hospital service when the client resides in the community. When

billed as an outpatient service, psychiatric-related services are billed separate from the medical components of the procedure.

Clinical Guidelines: Outpatient Electroconvulsive Treatment

The specified requirements for severity of need and intensity and quality of service must be met to satisfy the criteria for outpatient electroconvulsive therapy (ECT).

I. Severity of Need

Criteria A, B, C, D, E and F must be met to satisfy the criteria for severity of need.

A. The clinical evaluation indicates that the patient has a DSM-IV Axis I diagnosis or condition that, by accepted medical standards, can be expected to improve significantly through medically necessary and appropriate ECT. Such diagnoses and conditions include, but are not limited to, Major Depression, Bipolar Disorder, Mood Disorder with Psychotic Features, Catatonia, Schizoaffective Disorder, Schizophrenia, Acute Mania, severe lethargy due to a psychiatric condition, and/or psychiatric syndromes associated with medical conditions and medical disorders.

B. The type and severity of the behavioral health symptoms are such that a rapid response is required, including, but not limited to, high suicide or homicide risk, extreme agitation, life-threatening inanition, catatonia, psychosis, and/or stupor.

C. Either:

- the patient has a history of inadequate response to multiple adequate trials of medications and/or combination treatments, including polypharmacy when indicated, for the diagnosis(es) and condition(s); *or*

- the patient is unable or unwilling to comply with or tolerate side effects of available medications, or has a co-morbid medical condition that prevents the use of available medications, such that efficacious treatment with medications is unlikely; *or*

- the patient has a history of good response to ECT during an earlier episode of the illness, *or*

- the patient is pregnant and has severe mania or depression, and the risks of providing no treatment outweigh the risks of providing ECT.

D. The patient's status and/or co-morbid medical conditions do not rule out ECT; for example; unstable or severe cardiovascular disease, aneurysm or vascular malformation, severe hypertension, increased intracranial pressure, cerebral infarction, cerebral lesions, pulmonary insufficiency, musculoskeletal injuries or abnormalities (e.g., spinal injury), severe osteoporosis, glaucoma, retinal detachment, and/or medical status rated as severe.

E. All:

- the patient is medically stable and does not require the 24-hour medical/nursing monitoring or procedures provided in a hospital level of care, *and*

- the patient has access to a suitable environment and professional and/or social supports after recovery from the procedure, e.g., one or more responsible caregivers to drive the patient home after the procedure and provide post procedural care and monitoring, especially during the index ECT course, *and*

- the patient can be reasonably expected to comply with post-procedure recommendations that maintain the health and safety of the patient and others, e.g., prohibition from driving or operating machinery, complying with dietary, bladder, bowel, and medication instructions, and reporting adverse effects and/or negative changes in medical condition between treatments.

F. The patient and/or a legal guardian is able to understand the purpose, risks and benefits of ECT, and provides consent.

II. Intensity and Quality of Service

Criteria A, B, C, D, E, F and G must be met to satisfy the criteria for intensity and quality of service.

A. There is documentation of a clinical evaluation performed by a physician who is credentialed to provide ECT, to include:

- psychiatric history, including past response to ECT, mental status and current functioning; *and*

- medical history and examination focusing on neurological, cardiovascular, and pulmonary systems, current medical status, current medications, dental status, review of laboratory tests including electrocardiogram, if any, within 30 days prior to initiation of ECT; *and*

B. There is documentation of an anesthetic evaluation performed by an anesthesiologist or other qualified anesthesiology professional, to include:

- the patient's response to prior anesthetic inductions and any current anesthesia complications or risks, *and*

- required modifications in medications or standard anesthetic technique, if any.

C. There is a medically necessary and appropriate individualized treatment plan, or its update, specific to the patient's psychiatric and/or medical conditions, that addresses:

- specific medications to be administered during ECT, *and*

- choice of electrode placement during ECT, *and*

- stimulus dosing using a recognized method to produce an adequate seizure while minimizing adverse cognitive side effects.

D. There is continuous physiologic monitoring during ECT treatment, addressing:

- seizure duration, including missed, brief, and/or prolonged seizures, *and*
- electroencephalographic activity, *and*
- electrocardiographic activity, *and*
- vital signs, *and*
- oximetry, *and*
- other monitoring specific to the needs of the patient.

There is monitoring for and management of adverse effects during the procedure, including::

- cardiovascular effects, *and*
- prolonged seizures, *and*
- respiratory effects, including prolonged apnea, *and*
- headache, muscle soreness, and nausea.

F. There are post-ECT stabilization and recovery services, including:

- medically supervised stabilization services in the treatment area until vital signs and respiration are stable and no adverse effects are observed, *and*
- recovery services under the supervision of the anesthesia provider with continuous nursing observation and care; monitoring of vital signs including heart, respiration; pulse oximetry; electrocardiogram if there is cardiovascular disease or dysrhythmias are detected or expected. Electrocardiogram equipment should be continuously available in the recovery area. Recovery services should include treatment of postictal delirium and agitation, if any, including the use of sedative medications and other supportive interventions.

G. The patient is released in the care of a responsible adult who can monitor and provide supportive care and who is informed in writing of post-procedure behavioral limitations, signs of potentially adverse effects of treatment or deterioration in health or psychiatric status, and post-procedure recommendations for diet, medications, etc.

Criteria for Continued Treatment

III. Continued Stay

Criteria A, B, and C must be met to satisfy the criteria for continued treatment.

A. Despite reasonable therapeutic efforts, clinical findings indicate at least one of the following:

- the persistence of problems that meet the outpatient electroconvulsive treatment Severity of Need criteria as outlined in I.; *or*

- the emergence of additional problems that meet the outpatient electroconvulsive treatment Severity of Need criteria as outlined in I; *or*

- that attempts to discharge to a less intensive treatment will or can be reasonably expected, based on patient history and/or clinical findings, to result in exacerbation or worsening of the patient's condition and/or status.

B. The treatment plan allows for the lowest frequency of treatments that supports sustained remission and/or prevents worsening of symptoms.

C. The treatment plan meets the Intensity and Quality of Service Criteria (II above).

Inpatient Electroconvulsive Treatment

Criteria for Authorization

The specified requirements for severity of need and intensity and quality of service must be met to satisfy the criteria for inpatient electroconvulsive therapy (ECT).

I. Severity of Need

Criteria A, B, C, D, E and F must be met to satisfy the criteria for severity of need.

A. The clinical evaluation indicates that the patient has a DSM-IV Axis I diagnosis or condition that, by accepted medical standards, can be expected to improve significantly through medically necessary and appropriate ECT. Such diagnoses and conditions include, but are not limited to, Major Depression, Bipolar Disorder, Mood Disorder with Psychotic Features, Catatonia, Schizoaffective Disorder, Schizophrenia, Acute Mania, severe lethargy due to a psychiatric condition, and/or psychiatric syndromes associated with medical conditions and medical disorders.[CC1]

B. The type and severity of the behavioral health symptoms are such that a rapid response is required, including, but not limited to, high suicide or homicide risk, extreme agitation, life-threatening inanition, catatonia, psychosis, and/or stupor.

C. Either:

- the patient has a history of inadequate response to multiple adequate trials of medications and/or combination treatments, including polypharmacy when indicated, for the diagnosis(es) and condition(s); *or*

- the patient is unable or unwilling to comply with or tolerate side effects of available medications, or has a co-morbid medical condition that prevents the use of available medications, such that efficacious treatment with medications is unlikely; *or*

- the patient has a history of good response to ECT during an earlier episode of the illness, *or*

- the patient is pregnant and has severe mania or depression, and the risks of providing no treatment outweigh the risks of providing ECT.

D. The patient's status and/or co-morbid medical conditions do not rule out ECT; for example; unstable or severe cardiovascular disease, aneurysm or vascular malformation, severe hypertension, increased intracranial pressure, cerebral infarction, cerebral lesions, pulmonary insufficiency, musculoskeletal injuries or abnormalities (e.g., spinal injury), severe osteoporosis, glaucoma, retinal detachment, and/or medical status rated as severe.

E. All:

- the patient is medic the patient does not have access to a suitable environment and professional and/or social supports after recovery from the procedure, e.g., one or more responsible caregivers to drive the patient home after the procedure and provide post procedural care and monitoring, especially during the index ECT course.

- The patient and/or a legal guardian is able to understand the purpose, risks and benefits of ECT, and provides consent.

II. Intensity and Quality of Service

Criteria A, B, C, D, E and F must be met to satisfy the criteria for intensity and quality of service.

A. There is documentation of a clinical evaluation performed by a physician who is credentialed to provide ECT, to include:

- psychiatric history, including past response to ECT, mental status and current functioning; *and*

- medical history and examination focusing on neurological, cardiovascular and pulmonary systems, current medical status, current medications, dental status, review of laboratory tests including electrocardiogram, if any, within 30 days prior to initiation of ECT; *and*

B. There is documentation of an anesthetic evaluation performed by an anesthesiologist or other qualified anesthesiology professional, to include:

- the patient's response to prior anesthetic inductions and any current anesthesia complications or risks, *and*

- required modifications in medications or standard anesthetic technique, if any.

C. There is a medically necessary and appropriate individualized treatment plan, or its update, specific to the patient's psychiatric and/or medical conditions, that addresses:

- specific medications to be administered during ECT, *and*
- choice of electrode placement during ECT, *and*
- stimulus dosing using a recognized method to produce an adequate seizure while minimizing adverse cognitive side effects.

D. There is continuous physiologic monitoring during ECT treatment, addressing:

- seizure duration, including missed, brief and/or prolonged seizures, *and*
- electroencephalographic activity, *and*
- electrocardiographic activity, *and*
- vital signs, *and*
- oximetry, *and*
- other monitoring specific to the needs of the patient.

There is monitoring for and management of adverse effects during the procedure, including::

- cardiovascular effects, *and*
- prolonged seizures, *and*
- respiratory effects, including prolonged apnea, *and*
- headache, muscle soreness and nausea.

F. There are post-ECT stabilization and recovery services, including:

- medically supervised stabilization services in the treatment area until vital signs and respiration are stable and no adverse effects are observed, *and*
- recovery services under the supervision of the anesthesia provider with continuous nursing observation and care; monitoring of vital signs including heart, respiration; pulse oximetry; electrocardiogram if there is cardiovascular disease or dysrhythmias are detected or expected. Electrocardiogram equipment should be continuously available in the recovery area. Recovery services should include treatment of postictal delirium and agitation, if any, including the use of sedative medications and other supportive interventions.

Criteria for Continued Treatment

III. Continued Stay

Criteria A, B, and C must be met to satisfy the criteria for continued treatment.

A. Despite reasonable therapeutic efforts, clinical findings indicate at least one of the following:

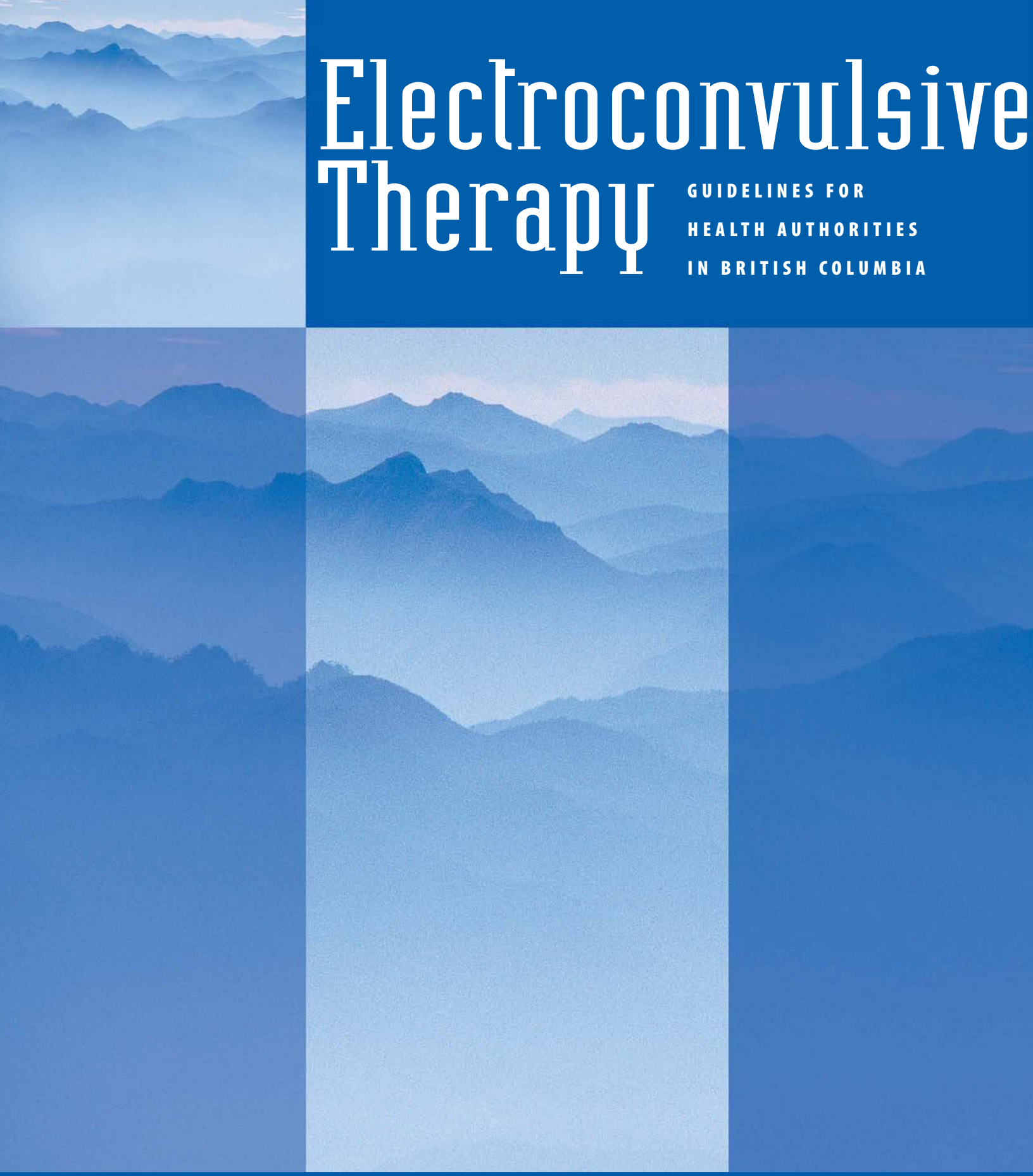
- the persistence of problems that meet the inpatient electroconvulsive treatment Severity of Need criteria as outlined in I.; *or*

- the emergence of additional problems that meet the inpatient electroconvulsive treatment Severity of Need criteria as outlined in I; *or*

- that attempts to discharge to a less intensive treatment will or can be reasonably expected, based on patient history and/or clinical findings, to result in exacerbation or worsening of the patient's condition and/or status.

B. the treatment plan allows for the lowest frequency of treatments that supports sustained remission and/or prevents worsening of symptoms.

C. the treatment plan meets the Intensity and Quality of Service Criteria (II above).



Electroconvulsive Therapy

GUIDELINES FOR HEALTH AUTHORITIES IN BRITISH COLUMBIA

Mheccu
Mental Health Evaluation & Community Consultation Unit

British Columbia
Ministry of Health Services

Electroconvulsive Therapy

GUIDELINES FOR HEALTH AUTHORITIES IN BRITISH COLUMBIA

APPLYING THE GUIDELINES

There is a great deal of evidence-based research on ECT, but clearly there is always much that needs to be researched. Patients present complex problems, and ECT is itself a complicated treatment. For both of these reasons, these guidelines should be considered recommendations rather than requirements, except when discussing legal mandates.

Professionals still need to tailor treatments to individual patient needs. Some latitude is also needed to make certain that professionals practicing in remote areas are not held to educational standards that are impossible to achieve.

Writers have been asked to use the word “should” when there is a strong belief that a particular issue must be adhered to. They have used softer words like “recommend” or “suggest” when they have felt more latitude is warranted.

Mheccu Mental Health Evaluation & Community Consultation Unit

British Columbia Ministry of Health Services

This report was funded by the Ministry of Health Services and carried out under contract with the Mental Health Evaluation and Community Consultation Unit (Mheccu).

Limited additional copies of this guide are available through Mheccu, besides digital versions on the websites of the Mental Health and Addictions, Ministry of Health Services and Mheccu:

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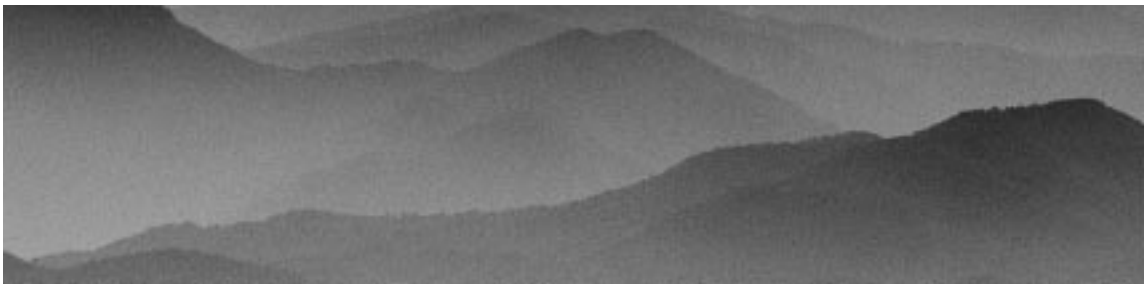

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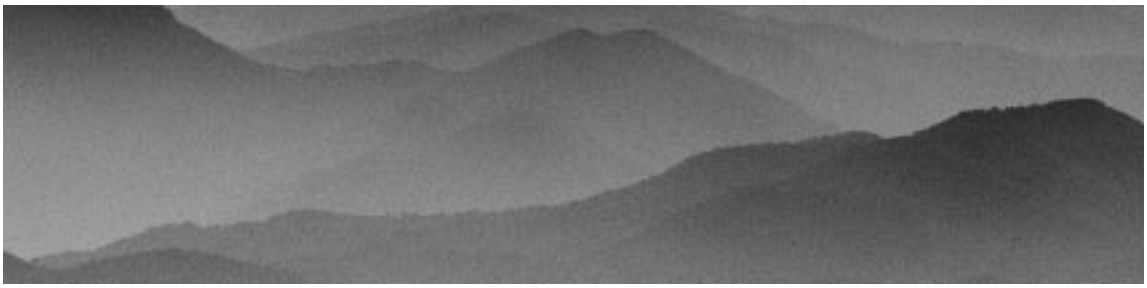

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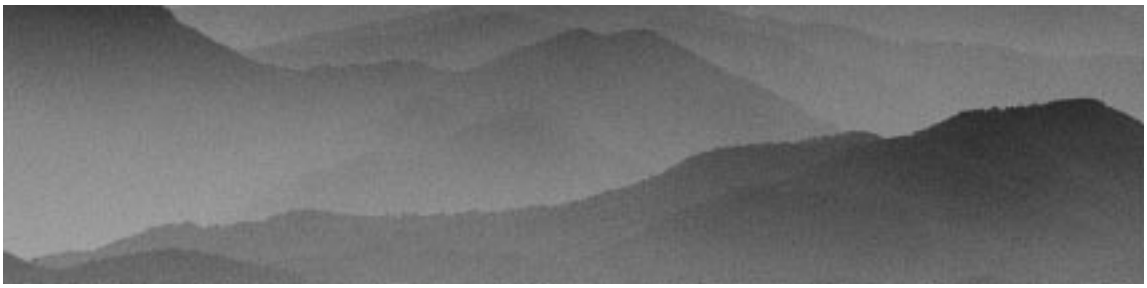


INTRODUCTION

The purpose of these guidelines for electroconvulsive therapy (ECT Guidelines) is to standardize the delivery of electroconvulsive therapy services across British Columbia. There will be differences in the way care is delivered according to local resources, but good basic care must be available wherever ECT is provided.

This introduction outlines the responsibilities of various sectors of the health care system for the delivery of ECT services, as well as how these guidelines were developed, their scope, and how they should be applied.

Responsibility for ECT Services

Responsibility for the delivery of ECT services rests primarily with health care professionals within a health authority. However, patients, families, and the Ministry of Health Services also have responsibilities, outlined below.

Ministry of Health Services British Columbia

Responsibilities are to

- Review and revise these guidelines, in consultation with health authorities, professions, and other stakeholders, every 5–7 years, depending on developments in the field.
- Establish in consultation with health authorities, methods of recording data about ECT services that make inter-facility comparisons useful for quality assurance purposes.
- Ensure that accurate information about ECT is made available to the public if public education on mental health treatments is provided by or through the Ministry.

Regional Health Authorities

Responsibilities are to

- Establish clear policies consistent with BC's ECT Guidelines.
- Appoint a psychiatrist in each regional health authority to be responsible for the ECT service.
- Appoint a nurse in each regional health authority to be responsible for ensuring nursing procedures are appropriate.
- Provide equipment and furnishings to make the procedures safe and user-friendly.
- Ensure staff are appropriately trained, and that there is a program of credentialing to administer ECT.
- Establish and carry out a quality assurance program that may include reviews of privileging, equipment, training, patient and family satisfaction, and comparisons with other health authorities.

Medical Staff

Responsibilities are to

- Ensure that there is a functioning privileging system for ECT, and that training and competency requirements consistent with these guidelines are established and maintained.
- Select appropriate patients, provide information to patients and obtain consent from patients and involve relatives according to good medical practice.
- Liaise with anesthetists, nurses, and other medical specialists as needed.
- Deliver ECT.
- Complete records.
- Participate in quality assurance activities relevant to ECT services.

Responsibility for ECT Services, continued

Nursing Staff

Responsibilities are to

- Ensure that nurses involved with ECT have appropriate training.
- Prepare patients psychologically and physically for ECT.
- Participate in the actual delivery of ECT, including preparation and aftercare.
- Provide education to patients and their families about ECT and the management of the illness it is treating.
- Participate in quality assurance activities relevant to ECT services.

Families and Other Caregivers

Responsibilities are to

- Support the patient before and after the ECT, by providing care and information.
- Understand information provided about ECT.
- Report progress or problems to caregivers if the patient and physician request.

Patients

Responsibilities are to

- Participate in their care as much as possible.
- Report positive and negative effects to caregivers.

Development of the Guidelines

The Ministry of Health Services contracted with the Mental Health Evaluation and Community Consultation Unit (Mheccu), to write guidelines for ECT in BC. A nine-person advisory committee was then created to give overall direction to and review the project. Members included a nurse, a representative from the Mood Disorders Association, academic psychiatrists from the University of British Columbia and the University of Toronto, as well as a clinical psychiatrist from Northern BC, and a BC Ministry of Health Services staff member. (See "ECT Guidelines Advisory Committee.")

To ensure guidelines were acceptable within the larger hospital community outside of Vancouver, psychiatric directors at all hospitals with mental health units under the *Mental Health Act* were then contacted and asked to share their hospital-specific guidelines, and to participate in reviewing the first draft.

Several additional consultations occurred before and after preparation of the first draft. This included consultations with the Consent Team for the Public Guardian and Trustee Office, the Health Care Consent and Care Facility Admissions Planning Group, the Mental Health Advocate for BC, the BC Psychiatric Association Executive, and Registered Nurses Association of B.C.

Contributing writers reviewed the Canadian Psychiatric Association position paper on ECT, the American Psychiatric Association's recommendations for ECT treatment, training and privileging (2001), and Australian and British guidelines for ECT. The writers also reviewed pertinent literature for their specific chapters, as well as Mheccu's ECT literature review.

Scope of the Guidelines

These guidelines cover patient and family education, clinical applications of ECT by physicians, nurses, and anesthetists, as well as suggestions for charting, professional education, and quality assurance programs.

Chapter 1: "Indications for Use" highlights the dominance of severe depression as the main indicator. Other indications such as mania and schizophrenia are also reviewed. Special population issues such as dementia and pregnancy are also addressed.

Chapter 2: "Patient Selection and Pre-ECT Evaluation" includes assessments that should be done in all cases, and those that may be done according to circumstances.

Chapter 3: "Patient Information and Consent" gives an overview of the laws regarding consent in BC for ECT, as well as information considered necessary for providing truly informed consent to patients and substitute decision-makers. It provides examples of information for patients and families.

Chapter 4: "Technique, Equipment, and Evaluation" focuses on patient preparation, the use of psychotropic medications with ECT, and required equipment. It also discusses the actual application of ECT, including skin preparation, electrode placement, seizure monitoring, and evaluation of individual courses of therapy.

Chapter 5: "Management of Adverse Effects" reviews the management of major side effects like postictal delirium, cognitive changes, and hypomania. It also offers suggestions for professionals facing patients who do not appear to be responding to the course of ECT.

Chapter 6: "Documentation of Individual Courses" outlines the basic pre-treatment and treatment parameters that need to be documented, illustrated with examples from the BC community.

Chapter 7: "Continuation and Maintenance ECT" discusses general indications for maintenance ECT, the process for administering it, and special considerations in patients who are suffering from dementia.

Chapter 8: "Nursing Considerations" discusses the role of the nurse in both inpatient and outpatient settings, as well as in the ECT treatment area.

Chapter 9: "Anesthesia Guidelines" reviews requirements for an anesthesic consultation before commencing ECT as needed. It also reviews the procedure used for ECT anesthetic, including the specific use of medications, and outlines the anesthetist's role in the post-anesthetic period.

Scope of the Guidelines, continued

Chapter 10: "Training and Privileging for Health Care Professionals" discusses guidelines for both nurses and physicians. It is recommended that the Head of the Department of Psychiatry (or equivalent), should be responsible for appointments, reappointment, monitoring, performance appraisals, and recommendations for privileging physicians to practice ECT.

Chapter 11: "Quality Assessment," gives recommendations for quality improvement (QI) activities, and for maintaining a standard database which should be kept for all patients receiving ECT anywhere in the province, in order for individual hospitals to appropriately evaluate their performance, and to facilitate inter-hospital comparisons of the provision of ECT.

Chapter 1

INDICATIONS FOR USE

General Considerations

Electroconvulsive therapy (ECT) is a safe and effective treatment for a variety of psychiatric and some medical conditions. It has proven superiority in prospective studies comparing ECT with "sham" ECT[1,2], and with standard antidepressant treatment in "medication-resistant" patients.[3,4] Especially when patients are identified early in the course of hospitalization and offered ECT as a treatment option, there can be a reduction in the length of stay and hospitalization cost, owing to both efficacy and rapidity of response.[5,6] There is no evidence to suggest that ECT response rates (found to be around 75 - 85% for mood disorders, but as low as 60 - 70% for those resistant to medication) drops off during the early or late parts of the lifespan. On the contrary, despite generally higher seizure thresholds in the elderly, evidence suggests that response rates are higher in both the "young" elderly (65 - 74),[7] and "old" elderly (75 or greater),[8,9] with fewer complications compared to certain antidepressants.[1] Nevertheless, ECT can induce side effects and may be physically risky for certain individuals, as is discussed in later chapters. Relapse rates after an acute course of ECT can be high without continuation or maintenance pharmaco-therapy and/or ECT.

Primary Indications for Use

As stated in the APA guidelines[1], there is "compelling data . . . or strong consensus" supporting the use of ECT in the following conditions:

Major Depressive Episode (arising from unipolar depression, as part of bipolar depression, or concomitant manic symptoms during "mixed states")

ECT should be strongly considered, especially when associated with one of the following features

- Acute suicidality with high risk of acting out suicidal thoughts.
- Psychotic features.
- Rapidly deteriorating physical status due to complications from the depression, such as poor oral intake.
- History of poor response to medications.
- History of good response to ECT.
- Patient preference.
- Risks of standard antidepressant treatment outweigh the risks of ECT, particularly in medically frail or elderly patients.
- Catatonia.

Mania

ECT should be particularly considered if

- Any of the above features is present.
- In the presence of extreme and sustained agitation.
- In the presence of "manic delirium."

Schizophrenia

According to the APA guidelines[1], the following associated features predict a favourable response to ECT

- Positive symptoms with abrupt or recent onset.
- Catatonia.
- History of good response to ECT.

Primary Indications for Use, continued

Studies demonstrating a favourable response to ECT in regard to psychotic symptoms have generally used a combination of ECT and standard antipsychotics.[10,11] There are reports that those with significant affective symptoms, whether arising from primary schizophrenia[12] or schizoaffective disorder,[13,14] can also benefit significantly from ECT. ECT for those with negative symptoms, or aggression unrelated to these conditions cannot be advocated at this time because of insufficient data.

Related conditions such as schizophreniform disorder can also respond favourably to ECT, but there is insufficient evidence to recommend ECT as being a primary treatment for brief psychotic disorder, which by its nature is considered time-limited. However during the course of brief psychotic disorder, ECT may be an option when the condition is considered life-threatening.

Secondary Indications for Use

Catatonia (unrelated to the primary conditions described above)
There should be a thorough medical and neurological work-up to identify reversible physical conditions in order to evaluate the risk for ECT and to initiate prompt medical treatment.

Parkinson's Disease

The motoric symptoms can improve, especially with associated "on-off" phenomenon. However, if an acute course of ECT is initiated, provisions should be considered for maintenance ECT in order to sustain a remission.[15,16] The attending physician should consider adjusting doses of anti-Parkinsonian agents during the course of ECT due to the possibility of treatment-emergent dyskinesia or psychosis.

Neuroleptic Malignant Syndrome

Antipsychotics should be discontinued and autonomic stability achieved[1] before initiating ECT.

Delirium

This should only be rarely considered for patients who require urgent treatment, after medical treatment has been initiated to target the specific cause.[1] For those who become delirious secondary to profound physical deterioration (e.g., dehydration) related to the underlying psychiatric disorder (e.g., depression), reversible physical factors should be corrected as quickly as possible before ECT to lessen risk, but the concomitant persistence of delirium should not necessarily impede the consideration of urgent ECT.

Intractable Seizure Disorder

Paradoxically, ECT can be considered when treating status epilepticus that is unresponsive to conventional treatments.[17]

Mood Disorder Secondary to Physical Conditions

Reversible underlying physical conditions should be adequately addressed first, in order to speed resolution of symptoms and lessen ECT risks.

Special Populations

Dementia

The efficacy of ECT when applied to those with dementia and concomitant mood disorder is under-studied. Clinical experience, case reports,[18] and retrospective case series[19] point to ECT being beneficial in mood, and sometimes cognitive, symptoms and signs in all stages of dementia. There are also case reports of ECT being successfully used for general agitation[20,21] or screaming[22,23] related to dementia without concomitant depression. However, without further evidence, promoting routine use of ECT for dementia without depression cannot be advocated at this time. It is strongly recommended to consider non-pharmacologic and pharmacologic approaches first.

Aging and dementia increase the likelihood of post-ECT delirium or transient worsening of cognitive impairment. Adjustment in technique (e.g., switch to unilateral or bifrontal ECT) and/or frequency of treatments (e.g., twice weekly instead of thrice weekly ECT) should be optimized to the clinical condition during the course, with special attention paid to tracking cognitive status.

Pregnancy and Postpartum Period

ECT is considered a safe and effective treatment in all stages of pregnancy.[24,25] Anesthesia consultation should be obtained well ahead of time because of potential differences in technique, monitoring, and positioning.[1] Obstetrical consultation is also suggested, particularly with high-risk pregnancy and those near term. Resources should be readily accessible in the event of a neonatal or obstetrical emergency.[1]

ECT is also considered a safe and effective treatment in the postpartum period. Anesthetic agents pose little risk to the nursing infant.[1]

Children and Adolescents

Sparse data exist on the use of ECT in adolescents, but available evidence suggests that ECT can be effective for treating the primary conditions outlined earlier (depression, mania, schizophrenia),[1, 26, 27, 28, 29, 30] or for catatonia.[27] Use of ECT in pre-pubertal children is even more rare, but has been successfully applied.[27,32]

Treating children and adolescents with ECT should be considered only when symptoms are severe, persistent, and significantly disabling.[31] Other parameters would include life-threatening symptoms and medication-resistant/intolerant patients. In the latter condition, since youths often do not adhere to medication regimes, the adequacy of medication trials needs to be scrutinized before embarking on a course of ECT.

Special Populations, continued

Children and Adolescents, continued

A second psychiatric opinion for the necessity of ECT by a clinician experienced in child and adolescent issues should be mandatory before proceeding.

Serious complications are rare.[27] ECT technique should take into account the younger person's lower seizure threshold on average.

Resource availability, consent, and psychiatric attitudes towards ECT for minors[33] are issues potentially limiting further study in this area. Nevertheless, ECT can reduce morbidity and mortality in this age group, just as in other age groups.

Congenital and Acquired Brain Injury

A number of case reports and case series exist describing ECT as being effective in the treatment of primary conditions described earlier and catatonia, without promoting persistent cognitive impairment for those with mental retardation[34,35] or traumatic brain injury.[36] There is a higher risk for post-ECT delirium, so adjustments in technique and/or frequency of treatments should be considered.

Cultural Considerations

It is important to understand the cultural context by which patients consent to or refuse ECT. There may be specific beliefs in certain cultures surrounding electricity and touching of the head that can prevent patients from accepting ECT as a form of treatment. Another barrier occurs in refugees and immigrants who may have experienced incarceration for political reasons in psychiatric institutions and who have been subjected to ECT involuntarily without psychiatric indication. Survivors of torture who have been subjected to electrical shocks may also resist the notion of ECT. The reluctance to proceed with ECT is unfortunate in these circumstances, since these individuals may benefit significantly from ECT in treating mood and psychotic disorders that have developed as a complication of trauma or migration.

Elderly Patients

Aside from physiological considerations during and immediately after anesthesia, being elderly in itself confers no specific risk for ECT, and may in fact predict a favourable response when compared to younger adults. However, being elderly increases the likelihood of dementia and having physical illness, which may in turn increase the risk for adverse effects due to ECT. For this reason, pre-operative evaluation is particularly important in the elderly, and an anesthesia consultation is often appropriate.

Other Conditions

There are insufficient data to advocate the use of ECT for such conditions as primary anxiety disorders, including post-traumatic stress disorder, or primary delusional disorder.[37] Those with chronic pain, along with concurrent affective symptoms, may experience an analgesic effect,[38] but this area requires further study. Studies[39,40] indicate that those with a personality disorder, particularly borderline type, can benefit if they have a concomitant Axis I mood disorder, but there is likely a reduced response rate overall, and a higher risk for relapse within one year. Drug-induced extrapyramidal symptoms have also been reported to improve transiently with ECT, but its role in this condition has not been firmly established.[12]

References

1. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001.
2. Brandon S, Cowley P, McDonald C, Neville P, Palmer R, Wellstood-Eason S. Leicester ECT trial: results in schizophrenia. British Journal of Psychiatry 1985; 146:177–183
3. Folkerts HW, Michael N, Tolle R, Schonauer K, Mucke S, Schulze-Monking H. Electroconvulsive therapy vs. paroxetine in treatment-resistant depression—a randomized study. Acta Psychiatrica Scandinavica 1997; 96:334–342
4. Lam RW, Bartley S, Yatham LN, Tam EM, Zis AP. Clinical predictors of short-term outcome in electroconvulsive therapy. Canadian Journal of Psychiatry 1999; 44:158–163
5. Markowitz J, Brown R, Sweeney J, Mann JJ. Reduced length and cost of hospital stay for major depression in patients treated with ECT. American Journal of Psychiatry 1987; 144:1025–1029
6. Olfson M, Marcus S, Sackeim HA, Thompson J, Pincus HA. Use of ECT for the inpatient treatment of recurrent major depression. American Journal of Psychiatry 1998; 155:22–29
7. Rubin EH, Kinscherf DA, Wehrman SA. Response to treatment of depression in the old and very old. Journal of Geriatric Psychiatry and Neurology 1991; 4:65–70
8. Manly DT, Oakley SP, Jr., Bloch RM. Electroconvulsive therapy in old-old patients. American Journal of Geriatric Psychiatry 2000; 8:232–236
9. O'Connor MK, Knapp R, Husain M, Rummans TA, Petrides G, Smith G, Mueller M, Snyder K, Bernstein H, Rush AJ, Fink M, Kellner C. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. American Journal of Geriatric Psychiatry 2001; 9:382–390
10. Chanpattana W, Chakrabhand ML, Kongsakon R, Techakasem P, Buppanharun W. Short-term effect of combined ECT and neuroleptic therapy in treatment-resistant schizophrenia. Journal of Electroconvulsive Therapy 1999; 15:129–139
11. Chanpattana W, Chakrabhand ML, Buppanharun W, Sackeim HA. Effects of stimulus intensity on the efficacy of bilateral ECT in schizophrenia: a preliminary study. Biological Psychiatry 1-8-2000; 48:222–228
12. Freeman C (ed). The ECT Handbook. The Second Report of the Royal College of Psychiatrists' Special Committee on ECT. London, Royal College of Psychiatrists, 1995.
13. Swoboda E, Conca A, Konig P, Waanders R, Hansen M. Maintenance electroconvulsive therapy in affective and schizoaffective disorder. Neuropsychobiology 2001; 43:23–28
14. Kramer BA. ECT in elderly patients with schizophrenia. American Journal of Geriatric Psychiatry 1999; 7:171–174
15. Wengel SP, Burke WJ, Pfeiffer RF, Roccaforte WH, Paige SR. Maintenance electroconvulsive therapy for intractable Parkinson's disease. American Journal of Geriatric Psychiatry 1998; 6:263–269
16. Aarsland D, Larsen JP, Waage O, Langeveld JH. Maintenance electroconvulsive therapy for Parkinson's disease. Convulsive Therapy 1997; 13:274–277
17. Lisanby SH, Bazil CW, Resor SR, Nobler MS, Finck DA, Sackeim HA. ECT in the treatment of status epilepticus. Journal of Electroconvulsive Therapy 2001; 17:210–215

References, continued

18. Weintraub D, Lippmann SB. ECT for major depression and mania with advanced dementia. Journal of Electroconvulsive Therapy 2001; 17:65–67
19. Rao V, Lyketsos CG. The benefits and risks of ECT for patients with primary dementia who also suffer from depression. International Journal of Geriatric Psychiatry 2000; 15:729–735
20. Holmberg SK, Tariot P, Challapalli R. Efficacy of ECT for agitation in dementia: a case report. American Journal of Geriatric Psychiatry 1996; 4:330–334.
21. Grant JE, Mohan SN. Treatment of agitation and aggression in four demented patients using ECT. Journal of Electroconvulsive Therapy 2001; 17:205–209
22. Carlyle W, Killick L, Ancill R. ECT: an effective treatment in the screaming demented patient. Journal of the American Geriatrics Society 1991; 39:637
23. Roccaforte WH, Wengel SP, Burke WJ. ECT for screaming in dementia. American Journal of Geriatric Psychiatry 2000; 8:177
24. Echevarria MM, Martin MJ, Sanchez VJ, Vazquez GT. Electroconvulsive therapy in the first trimester of pregnancy. Journal of Electroconvulsive Therapy 1998; 14:251–254
25. Bhatia SC, Baldwin SA, Bhatia SK. Electroconvulsive therapy during the third trimester of pregnancy. Journal of Electroconvulsive Therapy 1999; 15:270–274
26. Thorpe L, Whitney DK, Kutcher SP, Kennedy SH. Clinical guidelines for the treatment of depressive disorders. VI. Special populations. Canadian Journal of Psychiatry 2001; 46 Suppl 1:63S–76S
27. Rey JM, Walter G. Half a century of ECT use in young people. American Journal of Psychiatry 1997; 154:595–602
28. Duffett R, Hill P, Lelliott P. Use of electroconvulsive therapy in young people. British Journal of Psychiatry 1999; 175:228–30:228–230
29. Cohen D, Paillere-Martinot ML, Basquin M. Use of electroconvulsive therapy in adolescents. Convulsive Therapy 1997; 13:25–31
30. Kutcher S, Robertson HA. Electroconvulsive therapy in treatment-resistant bipolar youth. Journal of Child and Adolescent Psychopharmacology 1995; 5:167–175
31. Personal communication from Dr. S. Kutcher, Committee Member for the American Academy of Child and Adolescent Psychiatry's Development of Practice Parameters for "Use of ECT with Adolescents" (draft form)
32. Hill MA, Courvoisie H, Dawkins K, Nofal P, Thomas B. ECT for the treatment of intractable mania in two prepubertal male children. Convulsive Therapy 1997; 13:74–82
33. Ghaziuddin N, Kaza M, Ghazi N, King C, Walter G, Rey JM. Electroconvulsive therapy for minors: experiences and attitudes of child psychiatrists and psychologists. Journal of Electroconvulsive Therapy 2001; 17:109–117
34. Thuppal M, Fink M. Electroconvulsive therapy and mental retardation. Journal of Electroconvulsive Therapy 1999; 15:140–149
35. Aziz M, Maixner DF, DeQuardo J, Aldridge A, Tandon R. ECT and mental retardation: a review and case reports. Journal of Electroconvulsive Therapy 2001; 17:149–152

References, continued

36. Kant R, Coffey CE, Bogyi AM. Safety and efficacy of ECT in patients with head injury: a case series. Journal of Neuropsychiatry and Clinical Neuroscience 1999; 11:32–37
37. Fink M. Convulsive therapy in delusional disorders. Psychiatric Clinics of North America 1995; 18:393–406
38. Bloomstein JR, Rummans TA, Maruta T, Lin SC, Pileggi TS. The use of electroconvulsive therapy in pain patients. Psychosomatics 1996; 37:374–379
39. Sareen J, Enns MW, Guertin JE. The impact of clinically diagnosed personality disorders on acute and one-year outcomes of electroconvulsive therapy. Journal of Electroconvulsive Therapy 2000; 16:43–51
40. Debattista C, Mueller K. Is electroconvulsive therapy effective for the depressed patient with comor bid borderline personality disorder? Journal of Electroconvulsive Therapy 2001; 17:91–98

Chapter 2

PATIENT SELECTION AND PRE-ECT EVALUATION

Selection and Risk

Patient selection is critical in ensuring a high degree of confidence that ECT will be more effective than other treatments considered, while minimizing risk. Primary and secondary indications for ECT, including considerations for special populations, has been discussed in Chapter 1. ECT evaluation also addresses the presence of concurrent medical conditions that can increase risk, as well as the concurrent use of medical or psychiatric medications that can alter risk. The risk is defined as serious morbidity and mortality, which is most likely cardiopulmonary in nature if occurring,[1] and is considered in line with the risk associated with other low-risk procedures under a general anesthetic. While a wide range of mortality rates are reported in the literature, a widely-quoted figure derived by Kramer is 2/100,000 individual ECT treatments, yielding a figure of 1.6 deaths per 10,000 in a (typical) course of 8 ECTs.[2] This approximates the mortality figure of 1/10,000 quoted in the APA guidelines.[3]

Contraindications for ECT

There are no absolute contraindications for ECT.

ECT may be deemed necessary even when such "relative contraindications" identified by the APA guidelines,[4] are present

- Unstable or severe cardiovascular conditions, such as recent myocardial infarction, unstable angina, poorly-compensated heart failure, and severe valvular cardiac disease including critical aortic stenosis[5].
- Aneurysm or vascular malformation that might be susceptible to rupture with increased blood pressure.
- Increased intracranial pressure, as may occur with some brain tumors or other space-occupying cerebral lesions.
- Recent cerebral infarction.
- Pulmonary conditions such as severe chronic obstructive pulmonary disease, asthma, or pneumonia.
- Patient status rated as ASA (American Society of Anesthesiologists) level 4 or 5.

Conditions having substantially higher risk with ECT include

- Pheochromocytoma.
- Retinal detachment.
- Acute narrow angle glaucoma.

Those with cardiac pacemakers and implanted automatic defibrillators warrant some caution. It is unlikely ECT would disrupt the functioning of a modern cardiac pacemaker, but if uncertain, consult a cardiologist. The monitoring leads should be well grounded, and it is preferable **not** to have someone holding the patient who is grounded to the floor. Implanted automatic defibrillators are more susceptible to the effects of ECT during stimulation, thus a cardiologist and an anesthetist should be consulted well ahead of time.

Pre-ECT Evaluation

Other important concurrent medication should be considered prior to ECT (e.g., atrial fibrillation, diabetes, hypertension, and gastroesophageal disease), as addressed by the APA guidelines.[4] Other recent reviews explore ECT in those with cardiovascular conditions,[6] those with neurological conditions,[7] and those who are elderly.[8,9]

An adequate pre-ECT work-up should include the following, to be carried out within 10 days for inpatients or within 30 days for outpatients

- A physical examination.
- Evaluation of dentition for the presence of dentures and dental problems that could affect the use of the bite-block. Temporal-mandibular joint problems can also be noted.
- An electrocardiogram for those over age 45, or those with known cardiovascular disease.

Other routine lab investigations are not mandatory and should be guided by the patient's history and a physical exam. Common investigations include hemoglobin, electrolytes, and renal function tests.

The pre-ECT evaluation may also include

- A chest x-ray if there is a florid or unstable cardiopulmonary condition.
- A cervical spine x-ray in those with suspected cervical spine instability (rheumatoid arthritis, severe osteoporosis, Down syndrome, certain collagen vascular diseases) because it would warrant full muscle relaxation during ECT and monitoring the maximum relaxation time using a nerve stimulator.
- An anesthesia consult, strongly advised for those over age 60, those with significant cardiovascular or neurologic conditions, those who are pregnant, and those with potentially unstable cervical spine instability.
- A pertinent specialty consultation (e.g., cardiology, neurology), advised for medical conditions that would substantially increase the risk of ECT. Specialty consultation for special populations may also be indicated (e.g., obstetrics, pediatrics). An obstetrical consult well before the ECT is strongly advised for those who have high-risk pregnancies or are near term.

Pre-ECT Documentation and Referral

The following should be documented before ECT and conveyed to the ECT practitioner

- Indication for use of ECT.
- Comorbid psychiatric diagnoses.
- Concurrent medical conditions, highlighting those that can substantially enhance the risk of ECT
- Current medications.
- Whether a physical examination has been done within the recommended time frame, and the pertinent findings. A base-line blood pressure and pulse rate should be recorded as part of this physical examination.
- Whether consent was obtained, and who signed the consent (patient, patient's designated substitute decision-maker, public trustee, or medical director).
- Whether sample information about ECT was given to the patient and/or family.
- Whether an anesthetist was consulted, and if available, the ASA category.
- Copies of pertinent consultations by other specialists during the pre-ECT work-up.
- Whether the patient has a cardiac pacemaker or implanted automatic defibrillator.
- Dentition and the presence of dentures.
- Allergies.
- Base-line cognitive function (MMSE recommended).
- Any prior history of ECT and its outcome.
- The referring physician's or patient's preference for bilateral or unilateral ECT if requested, and a what frequency. However, ECT technique and frequency should be at the discretion of the ECT practitioner while considering these preferences and the clinical situation.
- The name and signature of the attending physician.

Documentation should clearly identify which medications should be held during each ECT treatment, which medications should be given on the morning of ECT, and which medications should be continued post-ECT.

References

1. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001, p16.
2. Abrams R. The mortality rate with ECT. Convulsive Therapy 1997; 13:125–127
3. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001, p320.
4. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001, Chapters 3,4,6.
5. Levin L, Wambold D, Viguera A, Welch CA, Drop LJ. Hemodynamic responses to ECT in a patient with critical aortic stenosis. Journal of Electroconvulsive Therapy 2000; 16:52–61
6. Journal of Electroconvulsive Therapy 1997; 13: Various papers.
7. Krystal AD, Coffey CE. Neuropsychiatric considerations in the use of electroconvulsive therapy. Journal of Neuropsychiatry and Clinical Neuroscience 1997; 9:283–292
8. Kelly KG, Zisselman M. Update on electroconvulsive therapy (ECT) in older adults. Journal of the American Geriatrics Society 2000; 48:560–566
9. Rabheru K. The use of electroconvulsive therapy in special patient populations. Canadian Journal of Psychiatry 2001; 46:710–719

Chapter 3

PATIENT INFORMATION AND CONSENT

All patients (and families, or substitute decision-makers where appropriate) must be given the opportunity to be adequately informed about ECT when it is recommended as a specific therapy. This chapter sets out guidelines on providing that information. A valid (informed) consent must be obtained from **voluntary** patients using the procedure set out in the *Health Care (Consent) and Care Facility (Admission) Act*. Most of the Act came into force in February 2000, and affects the provision of psychiatric and non-psychiatric treatment to adults (including those admitted to mental health facilities as voluntary patients), as well as the provision of non-psychiatric treatment to involuntary adult patients in mental health facilities. In the case of **involuntary** patients requiring ECT, the process for obtaining consent is set out in the *Mental Health Act* and must be followed.

Consent should not be viewed as simply filling in a form, but rather as a dynamic process that starts when the treatment is first recommended, and does not end until the therapy is completed. It should be an interactive educational process between patients (or their substitute decision- makers), and mental health professionals, where patients are respected as individuals with rights and needs, including the right to participate in decision-making and treatment planning and to have their questions answered.

The Law: Consent for Voluntary Patients

Under the Health Care (Consent) And Care Facility (Admission) Act[1]

The attending physician must obtain a valid consent from the patient, including completing an examination regarding their incapability to consent when there is evidence to support the possibility of incapability. It must be remembered that all patients are to be considered capable unless there is evidence to the contrary. Other health care professionals (i.e., nurses, psychiatric residents, or other students) may participate in the process of obtaining a valid consent by giving the required information to the patient. In the end, however, it is the sole responsibility of the attending physician (the physician who is overall in charge of the patient's psychiatric care) to ensure the process is completed properly. It is the responsibility of the treating physician (the physician doing the ECT) at the time of the individual treatments to ensure consent forms have been properly signed.

Consent is valid if the following criteria are met

- The consent that is given is for the health care that is being proposed.
- The consent is given voluntarily.
- The consent is not obtained by fraud or misrepresentation.
- The adult is capable of giving or refusing consent.
- The health care provider who wants to provide the treatment gives the adult the information a reasonable person would require to understand the proposed health care and make a decision about it, including information about
  - The condition for which the health care is proposed.
  - The nature of the proposed health care.
  - The risks and benefits of the health care that a reasonable person would expect to be told about, and any alternative courses of health care, including the option of not receiving the health care.
- The adult has been given an opportunity to ask questions and receive answers about the proposed health care.[2]

When deciding whether a patient is incapable of making a particular consent decision, a health care provider must base the decision on whether the patient demonstrates an understanding of the information given to him or her, and that the information applies to the patient's own health situation. Asking the patient to repeat the information in his or her own words or manner is one way of testing their understanding. Note that the symptoms of a patient's mental disorder may impair his or her capability to give a valid consent.

The Law: Consent for Voluntary Patients, continued

In all situations in which consent is required, the health care professional must consider the patient's communication needs and methods, and allow for interpretation or augmentative communication strategies when necessary, to ensure the patient has the best opportunity possible to understand and participate in decision-making.

If the patient is considered capable, the patient may accept or reject the ECT. If the patient is considered incapable of making a health care decision regarding ECT at the time the consent is being sought, then a second medical opinion is recommended in all circumstances. A second written opinion is **required** if a temporary substitute decision-maker (e.g., the patient's nearest relative) or a person named as the patient's representative in a representation agreement made under Section 7 of the *Representation Agreement Act* (a basic agreement containing only standard provisions) will be making the health care decision.

If the patient is considered incapable of making the health care decision, a substitute decision-maker must be sought. If the patient has a committee of the **person**, then the committee should be asked to make the decision. If the patient has an enhanced representation agreement made under Section 9 of the *Representation Agreement Act*, then that representative should be approached for a decision if he or she is authorized in the agreement to make health care decisions on behalf of the patient. A representative who is named in a basic agreement (i.e., a Section 7 agreement) and who has the authority to make health care decisions can make a decision as long as there are two medical opinions. In addition, if a representative with a "rep 7 agreement," or a temporary substitute decision-maker is making the decision, the *Health Care (Consent) and Care Facility (Admission) Act* states that an authorized advocacy organization must be notified (presently the Community Legal Assistance Society, or CLAS).

If there is neither a guardian nor a representative (under Sections 7 or 9), in place, a temporary substitute decision-maker must be chosen from a list of persons prescribed in section 16(1) of the *Health Care Consent and Care Facility (Admission) Act*. The health care provider must choose the first of the following who is available and qualified to act on the patient's behalf:

- The patient's adult spouse (including a common-law spouse or same sex partner).
- One of the patient's adult children.
- One of the patient's parents.
- The patient's adult brother or sister.
- Any other adult who is related to the patient by birth or adoption.

A person **may not** act as a substitute decision-maker for the patient unless they are at least 19 years of age (i.e., legally an adult in B.C.). In addition, the person must have been in contact with the patient during the preceding 12 months, must be capable of making the health care decision, must be willing to comply with the duties of a decision-maker (e.g., assisting the patient and complying with the patient's wishes expressed while capable), and must not be in a dispute with the patient.

The Law: Consent for Voluntary Patients, continued

Health care providers must not "shop" for substitute consent. The decision made by the substitute decision-maker who is first approached, and who is eligible to make the decision, is the decision that must be followed, even if the person refuses to give consent. If the decision is to refuse consent, the health care provider must not work down the list until he or she finds someone who will give consent.

If no-one is available or eligible to act as a temporary substitute decision-maker, then the health care provider must choose a person authorized by the Public Guardian and Trustee's office (PGT) (e.g., a friend of the patient, a relative-in-law), or an employee of the PGT.

If the guardian, representative, or temporary substitute decision-maker refuses treatment on the patient's behalf and a health care professional is concerned about the welfare of the patient because of this decision, then the health care professional can refer the decision to the Health Care and Care Facility Review Board. Patients, and all parties entitled to make decision on their behalf, can also refer decisions to give, refuse, or revoke consent to the Health Care and Care Facility Review Board.

The temporary substitute decision-maker makes the decision to accept or reject the treatment. The treatment must start within 21 days from the date on which the substitute makes this decision. The attending physician must immediately notify an authorized advocacy organization (presently CLAS), and the adult after the substitute has made the decision to consent to the ECT on the patient's behalf. In addition, there must be a 72-hour delay before the treatment is started, to allow the adult, family member, or advocacy organization to request a Review Board hearing regarding the decision if they so wish.

If there is no request for a Review Board hearing, then the treatment may proceed. If there is a request for a Review Board hearing, the hearing must occur within 7 days. The Health Care and Care Facility Review Board may confirm the decision under review, or substitute its own decision. The Review Board's decision may be appealed to the Supreme Court of BC within 30 days after a decision is made by the Board, during which time the treatment may not occur unless the court makes an interim order authorizing treatment to prevent physical or mental harm to the patient. (See Appendix A for a flowchart reviewing the process of consent for a voluntary patient.)

It should be remembered that a person holding power of attorney and a committee of the estate have authority only over a patient's finances. They **do not** have the authority to make substitute health care decisions. Remember also that representation agreements and committeeships can involve the management of a patient's property and financial affairs, decisions about their personal care and health care, or both. Consequently, the health care professional must make certain that the substitute decision-maker has the necessary authority to make substitute health care decisions. It is advisable to ask for and to read a copy of the representation agreement or the court order appointing the committee.

The Law on Consent for Involuntary Patients: the Mental Health Act

(amendments in force November 15,1999)[3]

When an adult is admitted to a mental health facility as an involuntary patient, the attending physician has a responsibility to inform the patient regarding the appropriateness and risks of ECT, if it is a recommended therapy. If the patient is considered capable of making the health care decision, then the patient may give or refuse consent and sign the consent form (Form 5: see Appendix E). If the patient is considered incapable, the attending physician should discuss the case, either in writing or orally, with the director of the facility, or his or her designate. That person may sign a Form 5 – a substitute consent – for the involuntary patient. Treatment may not proceed without a valid consent from the patient or valid substitute consent from a lawful substitute.

The assessment of incapability, under the *Mental Health Act* involves the attending physician informing the patient of the nature of their condition, as well as the reasons for and likely consequences of the proposed treatment. To be considered capable of making the health care decision under the *Mental Health Act*, the patient must demonstrate that he or she appreciates the nature of their condition, the reasons for treatment and its likely consequences.

When an adult is to receive treatment as an involuntary patient under the *Mental Health Act*, it may be helpful and appropriate to ask a family member, friend, or other person supportive of the patient to be involved in the informational process associated with obtaining a valid consent, in order to assist the patient throughout the course of ECT in understanding the procedures that are followed. (See Appendix D for a flowchart reviewing the process of consent for involuntary patients).

The *Mental Health Act* does not require a second medical opinion. However, it is recommended that a second medical opinion be obtained wherever possible when a decision to do ECT is first made, to ensure that the patient receives the most appropriate treatment.

Section 31 (2) of the *Mental Health Act* permits a patient, or someone acting on his or her behalf, to request a second medical opinion regarding the appropriateness of the treatment. A second medical opinion can be requested once per renewal period (at 1 month, 2 months, 3 months, and every 6 months thereafter). The second medical opinion is documented on Form 12 (See Appendix F). The director of the designated facility is required to sign the form to indicate that he or she has received the report. Following the receipt of the second medical opinion and discussion with the consulting physician, the director must consider whether changes should be made to the patient's authorized treatment. It should be noted that if a patient is released on extended leave, psychiatric treatment authorized by the director is still deemed to be given with the consent of the patient. This applies to patients receiving maintenance ECT upon discharge. If an involuntary patient on extended leave requires non-psychiatric treatment, the procedure for obtaining consent or substitute consent is the procedure set out in the *Health Care (Consent) and Care Facility (Admission) Act* for any adult who requires health care.

Repeat or Renewed Consents

Generally patients respond in 6 – 12 treatments for an index course. In certain cases, patients may require a substantial number of treatments to improve. It is recommended that if a patient does not show significant response after 15 treatments of an index course, another medical opinion should be sought at that time regarding the appropriateness of continuing the therapy. In fact, there is some support for the view that another medical opinion should be considered if the patient shows no response after a slightly lesser number of treatments. At all times along a course of ECT, it is necessary to check repetitively the patient's (or the substitute decision-maker's) understanding of the rationale for the treatment, and this person's continuing consent. If after one or more treatments a voluntary patient refuses to continue or withdraws consent, that position must be accepted. Once informed consent is withdrawn, a new informed consent must be obtained before continuing.

It is recommended for maintenance ECT that a renewed consent is obtained after either 6 months or every 15 treatments. This should be established policy by each hospital.

Knowledge of Adverse Side Effects

Health care professionals are encouraged to read Chapter 5, "Management of Adverse Effects," in *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging* (2nd edition), a Task Force Report of the American Psychiatric Association published in 2001. This is a very thorough literature review, with up to date references, and is considered the best resource on this topic.[4]

Giving Information to Patients or Substitute Decision-Makers for Consent

A health care professional must directly communicate information orally to the patient and/or the substitute decision-maker. It is recommended that a standard package of written information be given to all patients so that they can take it away and look at it privately, at a later time. (See Appendices G and H.) It may be prudent to have a videotape of ECT information available for the patient and family to observe. Either a physician or a nurse should answer any patient, family, or substitute decision-maker's questions after they have viewed the video.

Information given to patients and/or their substitute decision-makers should allow them to make an informed decision. The patients must be told why ECT is being considered for them at this time. They must be given information about ECT in general, and how the treatment is provided in a particular treatment setting, in a way that is sufficiently clear for them to understand given their educational backgrounds and learning styles. They also must be given sufficient time to think about the options and discuss them with their closest friends, relatives, and health care team.

There are three different types of information that should be given to all patients in proposing a recommended course of ECT

- A standardized general information package about ECT (see Appendix G).
- A list of recommended ECT information resources, including internet sites, books and videos (see Appendix G).
- A standardized hospital-specific information package about practical issues surrounding the administration of ECT. (See the following section for guidelines.)

Guidelines for Standard Hospital-Specific Information Packages

Patient information packages individualized for specific hospitals are recommended for giving practical information about the administration of ECT. Having information with the hospital logo on it personalizes the treatment for patients, and hospitals may also wish to have very specific guidelines for their own patients. These information packages should be written in plain language, in either 12- or 14-point print. The following is a list of items considered essential for appropriate education for patients regarding ECT

- Usual booking times and days for inpatients, or the place to come and the time to show up for outpatients, including the days.
- Hospital-specific requirements for taking nothing by mouth before ECT
- Requirements to wear no nail polish, jewelry (except rings), or contact lenses, and not to bring contacts or glasses to the treatment suite or OR
- Instructions regarding the administration of medications the night before and the morning of ECT.
- Instructions to empty one's bladder directly before going into the treatment area.
- The use of preoperative medications.
- The procedures carried out within the treatment suite or OR, including having an IV started; a blood pressure cuff put on; and ECG leads, EEG leads, and the stimulus band applied.
- The recovery room process, including monitoring of vital signs, as well as the approximate time for inpatients and outpatients to recover before going back to their rooms, or being allowed to go home.
- Post-discharge information for outpatients, including requirements to have a responsible person drive them home, not to drive or drink any alcohol for 24 hours, and to rest for a specific period on the day of the ECT.
- Instructions to patients about speaking to their nurse or their attending physician about any questions they may have about the procedure, and the importance of telling the nurse and the doctor about all side effects or perceived benefits from the treatments.

For an example, See Appendix H, Vancouver Hospital's Patient Information Booklet.

Consent Forms

It is recommended that general consent forms for procedures within a particular hospital be used. It is not necessary to develop a specific form for ECT because the important part of informed consent is the interactive informational process and its documentation.

Documentation of Informed Consent

It is necessary for all health care professionals involved in the process of obtaining informed consent to briefly document in the patient's chart what information has been given, and what the outcome of the discussions have been regarding acceptance or rejection of the treatment. All of the patient's questions must be answered, but not necessarily documented. The fact that the patients have received written information should also be documented. If patients view videos, this should be documented as well.

The conclusion of the competency assessment must be documented. If the patient is considered not competent, the basic reasons for this determination should be given

Contacting the Public Guardian and Trustee

The Health Care Decisions Office is based in Vancouver, and may be reached at (604) 775-0775, toll free at 1-877-511-4111, by fax at (604) 775-0777. If a health care professional needs more information about the process of consent under the *Health Care (Consent) and Care Facility (Admission) Act*, this office will be helpful in directing them to the appropriate resource. The Public Guardian and Trustee Website may also be helpful: www.trustee.bc.ca.

Consent for Patients under Nineteen Years of Age

Changes to the provincial *Infants Act* (R.S.B.C., 1996, c. 223),[5] which came into force in early 1993, removed the minimum age below which a young person or minor (someone under 19, known as "infant" in legislation) could not give or refuse consent to his or her own health care. Now each case must be assessed on the basis of the young person's capacity to understand information being given to him or her by a health care provider at the time health care is being proposed. This is sometimes referred to as the "mature minor" test. The majority of jurisdictions in Canada have adopted it.

Consent for Patients under Nineteen Years of Age, continued

Consent can be obtained from a young person only if the health care provider proposing to give health care has both

- Explained to the young person, and is satisfied, that he or she understands the nature, consequences, and the reasonably foreseeable benefits and risks of the health care.
- Made reasonable efforts to determine, and has concluded, that the health care is in the young person's best interests.

If in the opinion of the health care provider the young person does not understand the information being given about the proposed health care, substitute consent must be obtained from the young person's parents or legal guardian.

In general, the younger the person is, the more likely it is that parental consent will be required because the young person lacks the maturity to make his or her own decision. If a young person who is capable gives consent for the health care provider to inform his or her parents or legal guardian, this should not be viewed as the equivalent of a parental authorization or consent. **If the young person is capable of making the health care decision, he or she is the only person who can give (or refuse) consent, regardless of what a parent might say.**

In some cases, health care providers may not be prepared to provide treatment unless parents are involved and agree with the decision. While this might be good practice, the *Infants Act* does not now require it. Young people who are mature enough to make their own health care decisions are entitled to make those decisions without parental interference,[6] provided that the proposed health care is deemed to be in their best interests.

Section 17 of the *Infants Act* is the source of the proviso that young persons may consent only to treatment that is in their "best interests." This does not include inappropriate or unnecessary treatment. Generally speaking, "best interests" means that the health care must be given in the expectation that it will improve (or prevent deterioration or impairment of) the young person's physical or psychological health. If a health care provider has doubts about whether proposed health care would be in the young person's best interests, a second opinion should be obtained.

Young people under the age of 19 can be admitted involuntarily to a mental health facility under the *Mental Health Act*. In these circumstances, the *Mental Health Act* provides for substitute consent to **psychiatric treatment** to be given by the director of the facility following the same procedure, and using the same form (Form 5: see Appendix E) as for adult involuntary patients. If the young person requires treatment **other** than psychiatric treatment, the *Infants Act* procedure must be followed.

Consent for Patients under Nineteen Years of Age, continued

The *Mental Health Act* provides direction on admitting children and youths, and protects their rights by providing for regular reviews and early access to the Review Panel. The *Mental Health Act* also provides for young persons under 16 years of age to be admitted to a mental health facility by their parents or guardian as voluntary patients if the admitting physician and director agree. Once a minor under 16 years of age is admitted on this voluntary basis, only **psychiatric treatment** may be given with the consent of the parents or guardian. If he/she requires non-psychiatric treatment, the *Infants Act* procedure must be followed.

Form 1, Request for Admission (Voluntary Patient) (see Appendix B), and Form 2, Consent for Treatment, (Voluntary Patient) (see Appendix C), must be filled out by the parent or guardian admitting a young person.

References

1. *Health Care (Consent) and Care Facility (Admission) Act*, RSBC 1996, Chapter 181.
2. *Ministry of Health and Ministry Responsible for Seniors. A Primer to British Columbia's New Health Care Consent Legislation: the Health Care (Consent) and Care Facility (Admission) Act*, March 2000.
3. Mental Health Act, RSBC 1996, Chapter 288. Amended 15 November 1999 (BC Reg 233/1999).
4. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001.
5. *Infants Act*, RSBC 1996, Chapter 223.
6. The Vancouver Hospital and Health Sciences Centre Consent Guidelines. February 2000.

List of Chapter 3 Appendices

Appendix A:
Consent in Major Health Care for Incapable Adults for Voluntary Patients – this has been amended for ECT. The original document is in the educational package created by the Public Guardian and Trustee's Office for Acute Care Consent.

Appendix B:
This is Form 1 of the British Columbia Mental Health Act 1996, which in that document is in Appendix D.

Appendix C:
This is Form 2 of the *British Columbia Mental Health Act 1996*, which in that document is in Appendix D.

Appendix D:
ECT Treatment Consent for Involuntary Patients – this algorithm was created for this document by Dr. M.L. Donnelly and Dr. John Gray.

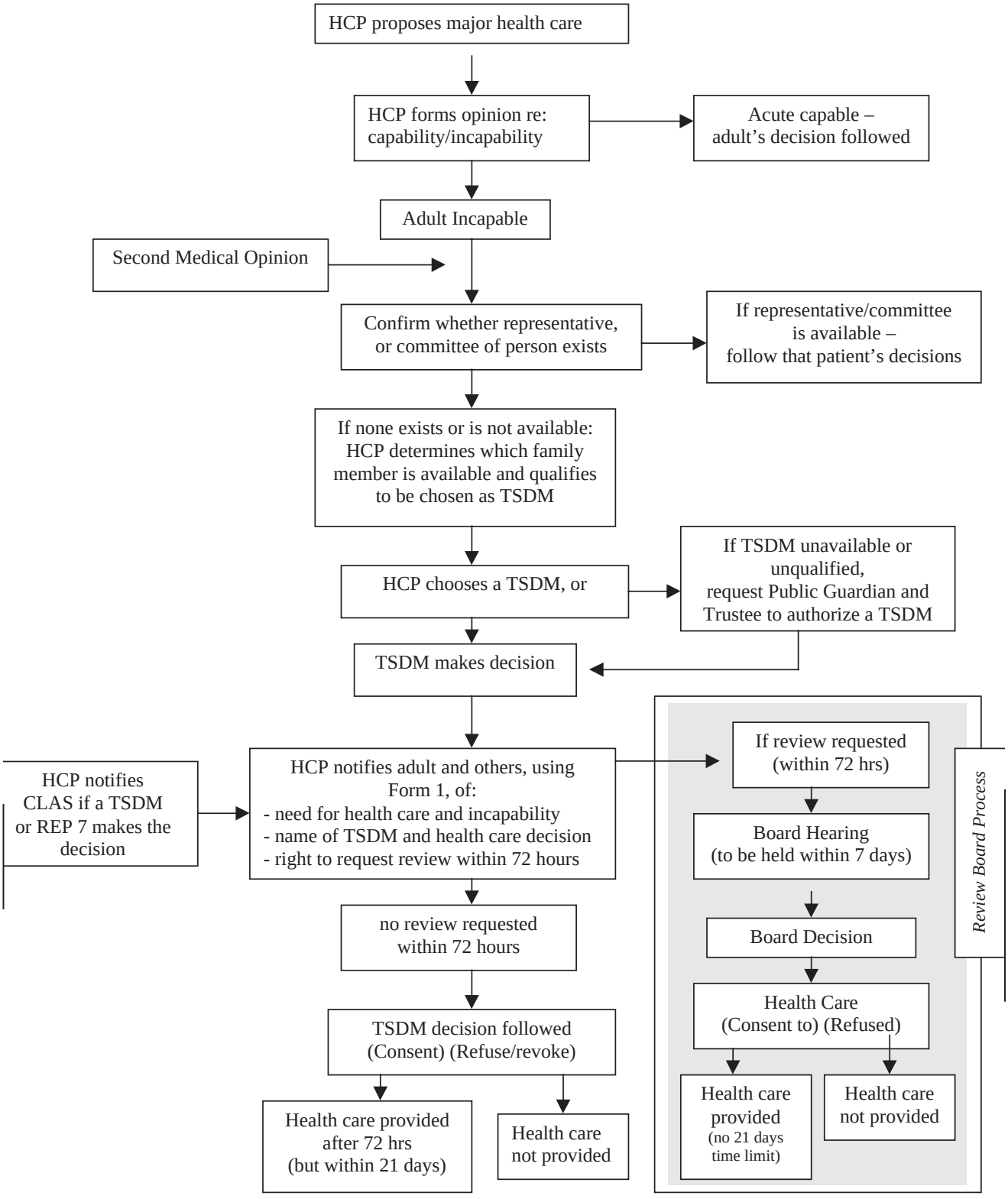
Appendix E:
This is Form 5 of the British Columbia *Mental Health Act 1996*, which in that document is in Appendix D.

Appendix F:
This is Form 12 of the *British Columbia Mental Health Act 1996*, which in that document is in Appendix D.

Appendix G:
Standard General Information Package General Information about Electroconvulsive Therapy (ECT). This was created for this document by Dr. M.L. Donnelly. This document can be photocopied and used in any way that is helpful.

Appendix H:
Electro-Convulsive Therapy (ECT) *Information Booklet*. This patient and family information booklet was created by Psychiatry Nursing and Education Services, University Hospital, Vancouver, revised by Marg Acton, Educator and Jeanette Eyre, ECT Coordinator UBC Hospital. Permission has been granted for this document to be used as is seen helpful, as long as the original development by Vancouver's University Hospital is cited in its use.

CONSENT IN MAJOR HEALTH CARE FOR INCAPABLE ADULTS FOR VOLUNTARY PATIENTS



BRITISH COLUMBIA

Ministry of Health and
Ministry Responsible for Seniors

FORM 1
MENTAL HEALTH ACT
[Section 20, R.S.B.C. 1996, c. 288]

REQUEST FOR ADMISSION (VOLUNTARY PATIENT)

The information on this form is collected pursuant to section 20 of the *Mental Health Act*. It will be used to document your voluntary admission to this facility designated under the *Mental Health Act*. Any questions you have about this form may be addressed to the director or staff of this facility.

I, _____ ,
patient's first and last name (please print)

of _____
street address *city* *province* *postal code*

request admission to _____
name of designated facility

for treatment, and agree to abide by the rules and regulations of the designated facility and to inform the staff if I wish to be discharged from the designated facility.

_____ _____
signature (patient, if 16 years of age or older) *date of signature (dd / mm / yyyy)*

OR

_____ _____
signature (parent or guardian, if patient is under the age of 16 years) *date of signature (dd / mm / yyyy)*

_____
name of parent or guardian, if applicable (please print)

_____ _____
signature (witness) *date of signature (dd / mm / yyyy)*

_____
first and last name of witness (please print)

BRITISH COLUMBIA

Ministry of Health and
Ministry Responsible for Seniors

FORM 2
MENTAL HEALTH ACT
[Section 20, R.S.B.C. 1996, c. 288]

CONSENT FOR TREATMENT (VOLUNTARY PATIENT)

I, _____ ,
patient's first and last name (please print)

in _____
name of designated facility

authorize the following treatment(s) _____

The nature of my condition, options for my treatment, the reasons for and the likely benefits and risks of the treatment(s) described above have been explained to me by _____.
name and position/title

_____ _____
signature (patient, if 16 years of age or older) *date of signature (dd / mm / yyyy)*

or

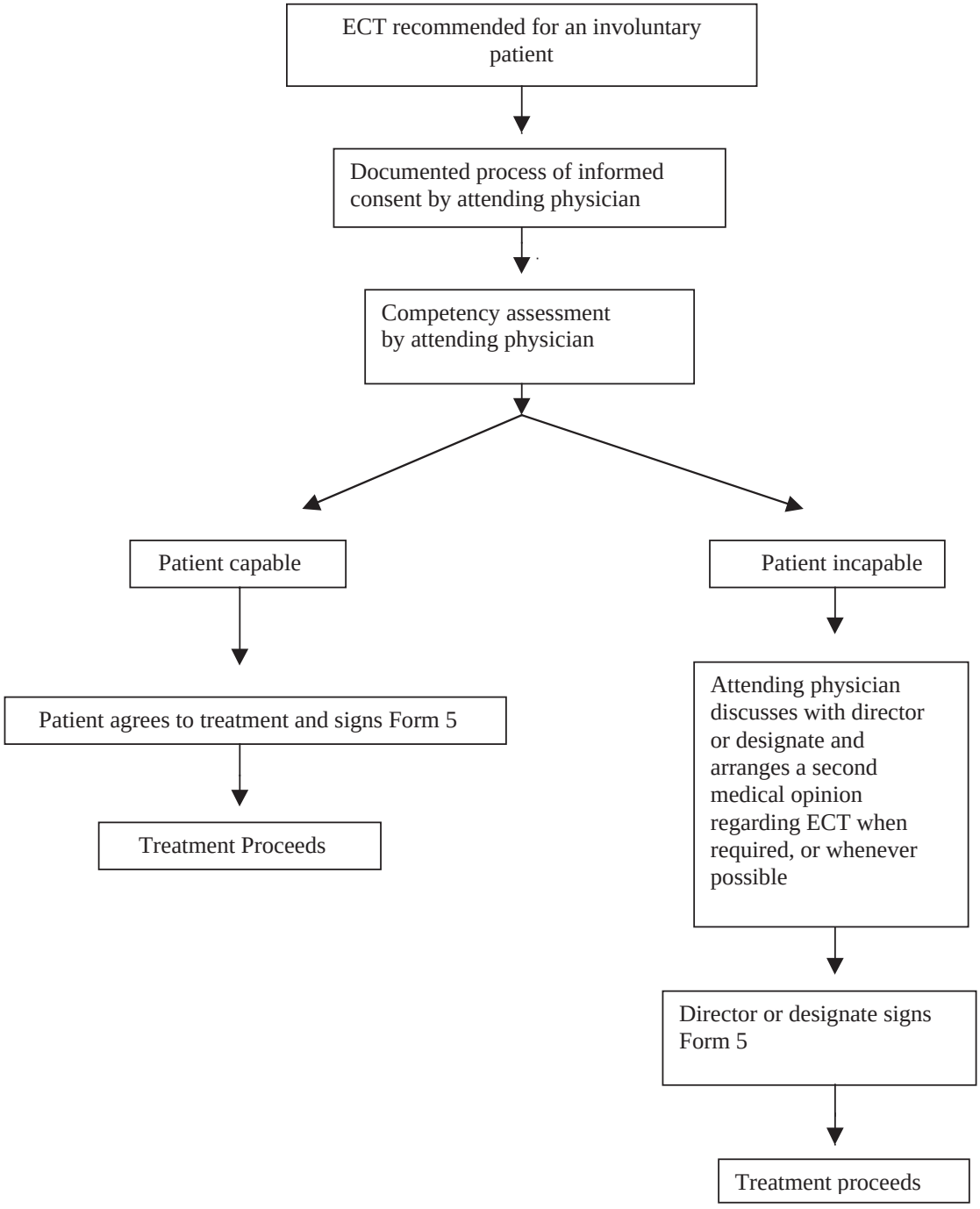
_____ _____
signature (parent or guardian, if patient is under 16 years of age) *date of signature (dd / mm / yyyy)*

name of parent or guardian, if applicable (please print)

_____ _____
signature (witness) *date of signature (dd / mm / yyyy)*

_____
first and last name of witness (please print)

ECT TREATMENT CONSENT FOR INVOLUNTARY PATIENTS



Note: A 2nd medical opinion may be requested by the patient, or substitute decision-maker once per renewal period, regarding appropriateness of ECT as a therapy.

BRITISH COLUMBIA
Ministry of Health and
Ministry Responsible for Seniors

FORM 5
MENTAL HEALTH ACT
[Sections 8 and 31,
R.S.B.C. 1996, c. 288]

CONSENT FOR TREATMENT (INVOLUNTARY PATIENT)

Note: Complete either A or B

A. I, _____ , authorize the treatment described below.
first and last name of patient (please print)

B. I, _____ , authorize the treatment described below
name of director or person authorized by the director (please print)

with respect to _____ at _____ .
first and last name of patient *name of designated facility (please print)*

Description of treatment/course of treatment:

_____

_____

_____

_____

_____

_____

_____

_____

_____

The nature of the condition, options for treatment, the reasons for and the likely benefits and risks of the treatment described above have been explained to me by _____ .
name and position/title

Complete either A or B

A. If signed by patient

_____
patient's signature

_____ _____
date (dd / mm / yyyy) *time*

_____
witness' signature

_____
witness' first and last name (please print)

To the best of my judgment, the above-named patient was capable of understanding the nature of the above authorization at the time it was signed.

_____ , M.D.
signature

B. If not signed by patient

_____
signature

_____
name of director or person authorized by the director (please print)

_____
position/title

_____ _____
date (dd / mm / yyyy) *time*

The above-named patient is an involuntary patient under section 22, 28, 29, 30, or 42 of the *Mental Health Act* and to the best of my judgment is incapable of appreciating the nature of treatment and/or his or her need for it, and is therefore incapable of giving consent.

_____ , M.D.
signature

BRITISH COLUMBIA

Ministry of Health and
Ministry Responsible for Seniors

FORM 12
MENTAL HEALTH ACT
[Section 31, R.S.B.C. 1996, c. 288]

MEDICAL REPORT
(SECOND MEDICAL OPINION)

To the director of _____ :
name of designated facility

On _____ I examined _____
date (dd / mm / yyyy) *first and last name of patient (please print)*

who is a patient at _____ .
name of designated facility (please print)

Based on my examination, my opinion on the appropriateness of the treatment is *(include recommendations if any)*:

_____

_____

_____

_____

_____

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_____

_____

_____

_____

_____

_____ _____
physician's signature *date (dd / mm / yyyy)*

_____
physician's name (please print)

_____
physician's address and phone number

For Office Use Only

☐ I acknowledge receipt of this medical report.

_____ _____
signature of director *date (dd / mm / yyyy)*

Standard General Information Package

General Information about Electroconvulsive Therapy (ECT)

What is ECT?

Electroconvulsive therapy (ECT) is a physical therapy in which a patient under general anesthetic will have an electrical current passed through his or her brain, causing a seizure in the brain. This therapy was developed in the 1930s and has become a painless, safe, effective therapy for a number of psychiatric problems.

How does it work?

Current theories suggest that the seizure activity causes changes in brain chemistry.

When is ECT used?

ECT is used primarily for depressive illnesses. It is usually reserved for situations where medications have not worked, but it may be the first choice of therapy for frailer, older patients for whom medications may be more of a problem. If a patient has responded well to ECT in the past, it may be his or her own first choice. ECT is also used occasionally in mania, schizophrenia, and in severe Parkinson's disease.

How is the procedure carried out?

Patients are treated in specific ECT suites or in hospital operating rooms. You will be given an intravenous line. Sensors monitoring your heart and brain waves will then be applied to your head, and you will be given a short-acting general anesthetic. Once you are asleep, you will be given a muscle relaxant. When you are completely asleep and your muscles are relaxed, a brief electrical current will applied to your brain either unilaterally (on one side), or bilaterally (on both sides). A brief seizure will follow, which will be modified by the muscle-relaxants so that medical staff may need to look carefully at brain wave monitors and observe your toe and hand movements to monitor it. The whole procedure takes only a few minutes. You will then be moved to a recovery area where a nurse will closely observe your pulse and blood pressure until you are awake enough to return to your room or to the outpatient clinic.

How many treatments are required?

Usually patients with acute psychiatric problems require 6 – 12 treatments, given either 2 or 3 times a week. Occasionally more treatments will be required for maximum benefit.

In order to keep patients well, outpatient maintenance ECT is sometimes recommended. In such cases the treating physician determines the number and frequency of treatments by assessing specific clinical problems and needs.

Standard General Information Package, continued

General Information about Electroconvulsive Therapy (ECT), continued

What are the benefits of ECT?

ECT has produced substantial improvement in most of the patients who have been treated with it. It has been shown to be effective in many who have not responded to other forms of treatment. In fact, between 50 – 70% of patients who previously did not respond to medications will respond positively to ECT.[1] Many depressed patients have problems with their memory; after their depression is relieved, which may occur after having ECT, their memory may improve.

Improvement is gradual over several treatments until most or all symptoms of a depression are relieved. You may notice an improvement of appetite early on, later an improvement in energy, and finally an overall sense of feeling better. The treatment team will work with you to monitor your individual symptoms and response.

What are the side effects?

Immediately after ECT, you may experience some nausea, headache, and muscle aches. These are most often managed by taking plain Tylenol tablets. You may experience some acute confusion on the day of the ECT treatment, which most often resolves quickly. You may also forget recent events or events occurring around the time that you have the ECT. These memory problems are usually minor and may be decreased by slight changes in the procedure. Some patients experience longer-lasting problems with recalling memories from around the time of the ECT, and occasionally problems recalling some distant events. These memory effects generally subside once the ECT is completed. A few patients may have more severe problems remembering events from the distant past. Patients generally have fewer memory problems with unilateral ECT compared to bilateral ECT. Your treating psychiatrist will further explain this.

You should always report possible side effects to your nurses or psychiatrist, so the treatment team can work to reduce them.

ECT is considered very safe, and no more dangerous than a minor surgical procedure requiring a short general anesthetic. A current estimate of mortality in ECT is 2 in every 100,000 treatments.[2] If you are worried about this, please discuss it with your psychiatrist.

Standard General Information Package, continued

General Information about Electroconvulsive Therapy (ECT), continued

How do I give consent, and what are my rights to withdraw consent?

Your treating physician will inform you about the reasons ECT is being considered as an appropriate therapy for you. You will also be informed about possible alternative treatments and will get the opportunity to ask questions about your proposed treatment. Your treating physician will request your informed consent by asking you to sign a consent form.

In circumstances where voluntary patients are not able to give their own consent, the physician will seek consent from a substitute decision-maker, in this order: their adult spouse, one of their adult children, one of their parents, one of their adult brothers or sisters, or any other adult related to them by birth or adoption. For involuntary patients, the medical director may be asked to give substitute consent. A second med Iical opinion can be requested about appropriateness of the treatment.

You or your substitute decision-maker may withdraw consent even after the treatments have started. The treating psychiatrist will arrange for appropriate alternative treatments.

What happens after ECT?

Your physician will discuss what treatments are suggested to keep you well after ECT has been completed. In most circumstances they will suggest the follow-up use of medications. In some situations, they may recommend a course of maintenance ECT to maintain improvement.

How can I find out more about ECT?

You can find out more about ECT by checking the following resources:

Internet sites

- The Royal College of Psychiatrists http://www.rcpsych.ac.uk/info/webguide/ect.htm
- The American Psychiatric Association http://www.psych.org/public_info/ECT~1.cfm
- American Academy of Family Physicians http://familydoctor.org/handouts/058.html
- The Mayo Clinic http://www.MayoClinic.com/home?id=HQ00612

Standard General Information Package, continued

Books

- *Electroshock: Restoring the Mind*, by Max Fink. New York: Oxford University Press, 1999. Riverview Hospital Library Call no. WM/412/F56/1999
- *Holiday of Darkness* by Norman S. Endler (revised edition). Toronto: Wall and Thompson, 1990

Videos (available at Riverview Hospital Library)

- Electroconvulsive Therapy: ECT: The Treatment, The Questions, The Answers by Leon Grunhaus, Lisa Barroso-Whal. Ann Arbor, Mich: University of Michigan, 1988. Call number: WM/412/G78/1988
- Electroconvulsive Therapy: Information for Patients and their Families by American Medical Communications. American Medical Communications, 1997 Call number: WM/41/E53/1997
- Informed ECT for Patients and Families, with Dr. Max Fink by Max Fink (15 min.). Lake Bluff, Ill.: Somatics, 1986. Call number: WM/412/I53/1986

References

- Rabheru K. The use of electroconvulsive therapy in special patient populations. Canadian Journal of Psychiatry 2001; 46:710–719
- Abrams R. Convulsive Therapy 1997; 13:125–127

Electro-Convulsive Therapy (ECT)

Information Booklet

VANCOUVER HOSPITAL
& Health Sciences Centre

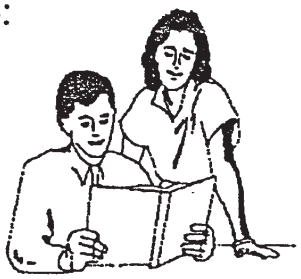
We hope this booklet is helpful in assisting you to understand Electro-Convulsive Therapy (ECT) and the part it plays in the treatment of your illness.

As you read through, we suggest you write down any questions on the pages provided and discuss these with your doctor or nurse.

TABLE OF CONTENTS

Introduction

This booklet has been prepared for the patient whose physician has recommended ECT for treatment. It has been designed to complement the teaching offered. After the teaching sessions you will be able to:



- ➢ Discuss ECT as an effective mode of treatment
- ➢ Discuss what will take place prior to the first treatment
- ➢ Discuss what will take place before, during and after each treatment
- ➢ Identify the 5 most common side effects of ECT and describe ways to cope with each
- ➢ Identify 3 possible methods of follow-up to ECT

Current medical literature states that ECT is a safe & effective procedure for which there continues to be an established clinical need.

What is ECT treatment like?

You will be given an anaesthetic to put you to sleep followed by a muscle relaxant. Brief electric currents are then passed through electrodes on the scalp to stimulate the brain. Stimulation of the brain causes a mild seizure (convulsion), that is of brief duration. You will not be aware of anything because you will be asleep. When you waken, you will be in the recovery room where nursing staff will be caring for you.

1

The electric current can be applied in 2 ways:

a) **Unilateral** - 2 electrodes applied on one side of the head

b) **Bilateral** - 2 electrodes applied; one on either side of the head

In consultation with you, your physician will decide the number, frequency and method of your treatments.

How does ECT work?

Current theories suggest that the seizure activity causes changes in brain chemistry.

Who needs ECT?

➢ The depressed person who is not responding to other treatment or who is at increased risk for suicide.

➢ The depressed elderly person who cannot take medication due to risk of side effects.

➢ The person experiencing delusional thinking (fixed, false beliefs) or hallucinations (e.g. hearing voices when no one is there) who is not responding to medication.

➢ The person with Parkinson's Disease, who is:

- suffering from psychiatric side effects of their medication
- depressed
- requiring treatment for the illness

(Note: see Appendix I)

➢ The person with mania who is not responsive to treatment.

2

➢ The person with physical symptoms and chronic pain for which there is no identifiable cause (somatization) who fails to respond to medication.

ECT can be the:

❖ ***Safest Method of Treatment***
(e.g. pregnant women; the elderly)

❖ ***Fastest Method of Treatment***
(e.g. mood/delusions may improve in 2 weeks, whereas with medication mood/delusions may take 3-4 weeks to improve.)

Facts Versus Myths

Fact: **ECT performed today is safe and effective. Prior to the first treatment, the physician completes a thorough physical examination. Before each treatment, you are given an anaesthetic and muscle relaxant.**

Myth: ECT is a "Barbaric & Archaic" form of treatment.

Fact: **Memory loss may occur in varying degrees lasting from a few days to a few months. This will usually not be permanent. However, memory loss for events that occur before, during, and/or after the period of time you are being treated may persist. It is recommended that important decisions be postponed during this time.**

Myth: ECT leaves permanent memory loss.

Fact: **ECT has been found to be as effective or more effective than medication.**

Myth: ECT is less effective than other types of therapy.

3

What will happen prior to my first treatment?

➢ **Consent** - your doctor will explain the procedure and request that you sign a consent form.

➢ You may be visited by some or all of the following people. We recommend that you write down any questions you may have for each one:

- The doctor who will be giving your anaesthetic;
- The doctor who will be giving your treatment;
- The nurse who is in charge of the Treatment Area *(UBC Site)*.

➢ You will be encouraged to attend the "ECT Group" for support and information. Ask your nurse for details *(UBC Site)*.

What will happen before, during and after each treatment?

➢ **NIGHT BEFORE**

Bath/Shower and Shampoo

- Aids in relaxation & promotes sleep;
- Clean hair provides for better conduction of the electric current;
- It is important that hair be dry before treatment is given, therefore hair should be washed the night before;
- The gel used with the electrodes leaves a sticky residue, you may prefer to shampoo after each treatment.

Wearing Hospital Clothing

- This is necessary to prevent possible soiling of personal clothing.

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Remove Nail Polish and Make-up

- This allows for better assessment of your physical condition during the anaesthetic.

Ensure Valuable Jewellery is Locked Up

- rings can be taped in place and worn during treatment.

Inpatients:

- you can ask your nurse to place valuables in a safe place in the nursing station.

Outpatients:

- please DO NOT bring valuables.

Nothing to Eat or Drink After Midnight the Night Before (NPO)

- This includes candy, gum & water.
- This is to prevent aspiration of food if vomiting occurs during or after treatment.

Inpatients:

- Food and beverages will be removed from your bedside area; they will be returned when your treatment is finished.

Treatment Time

- You will be informed the day before of the time your treatment is scheduled. (On Friday for Monday treatment)
- Treatments are Monday, Wednesday and Friday during the morning.

Outpatients:

- You will also be informed of:
  - the time to arrive at the hospital.
  - your expected time of discharge.

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Medication

- Sometimes a medication will be given the night before and/or the morning of your treatment. Ask your nurse about the specific reason for this.

Identification (I.D.) Bands

Inpatients:

- If you remove your I.D. band when you go out on a pass, please ensure you are given a new one prior to going for treatment.
- If you have drug allergies, it is essential to wear a band indicating what these are.

➢ MORNING OF TREATMENT

On Ward/Outpatients

Nothing to Eat or Drink until After Your Treatment*

Reminder: This includes candy, gum & water.

Vital Signs

- Temperature, pulse, respirations and blood pressure will be taken prior to your treatment.

Dentures

- You will be asked to remove your dentures before receiving the anaesthetic. You can wear them to the treatment area/operating room, provided you take a container with you to put them in (UBC Site only).

Glasses/Contact Lenses

- You will be asked to remove your glasses/contact lenses. If you wish to wear your glasses to the treatment area, please bring your glass case with you (UBC Site only).

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Bladder

- You will be asked to empty your bladder about 15 minutes prior to your treatment. This is to avoid incontinence during the treatment.

Medication

- Occasionally a medication will be given 1-2 hours prior to your treatment. This will be taken with a small sip of water. Your regular medications will usually be held and given to you after your treatment is finished.

Escort

- You will be accompanied to the Treatment Area (UBC Site) or to the Operating Room Area (VGH Site) approximately 5-45 minutes prior to your scheduled time of treatment.

Outpatients:

- Consider having a responsible adult accompany you to the hospital.
- Be prepared to be at the hospital for up to 4 hours.

➢ AFTER EACH TREATMENT

Recovery Room

- Following your treatment you will be moved on a stretcher to the Recovery Room while still asleep. You will remain there for approximately 10-30 minutes (UBC), 60 minutes (VGH).

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When you awaken you will find nurses in attendance who carry out the following procedures:

- blood pressure, pulse and respirations taken every 5-10 minutes
- oxygen is given by mask or nasal prongs.
- a heart monitor may be used to provide nursing staff with information about your heart beat.
- nurses will be asking you for your name and if you know where you are. This is to assess your level of consciousness.
- nurses will ask you to grip their hand and lift your head off the pillow. This is to assess muscle strength.
- a needle inserted in your vein which was used to give you your anaesthetic will be removed. A bandaid may be applied to the area. This can be removed at your discretion.

Inpatients:

- you will be returned to your own room by wheelchair or stretcher.

Outpatients:

- you will be allowed to rest until you are fully awake.
- breakfast will be provided prior to discharge.

<u>On Ward</u>

Inpatients:

When you first return your nurse will assist you to bed and will take your blood pressure, pulse, and respirations. The nurse will assess your level of recovery from the anaesthetic. Once you are fully awake you will be encouraged to get up, get dressed and have breakfast.

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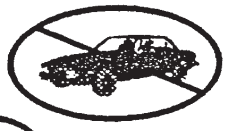
Outpatients: Discharge Information - What do I need to Know?

You have had a general anaesthetic and the effects persist for many hours. The following precautions are advised by your anaesthetist and psychiatrist:

1. Have a responsible adult pick you up from the Recovery Room and stay with you for the first 24 hours.
2. Rest quietly at home for the remainder of the day.
3. DO NOT drive your car for at least 24 hours.



4. DO NOT drink alcohol for 24 hours.

5. DO NOT travel alone for the rest of the day.

What are the 5 Most Common Side Effects?

1. **Muscle Stiffness**
   Caused by the medication given to relax your muscles.

   Ways to relieve
   - inform your nurse or doctor.
   - take a warm bath.
   - request medication for pain.
   - do some moderate exercises, e.g. walking.

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2. **Confusion**
   You may be temporarily confused or disoriented (i.e. not know the date or time) due to the effects of the anaesthetic or treatment.

   Ways to relieve
   - seek reassurance from staff.

Caution:
If you plan to go on a pass on the day of treatment, you must be accompanied by a responsible adult.

3. **Memory Loss**
   Because temporary memory loss is a common side effect of ECT it is recommended that you postpone major decision making.

   Ways to relieve
   - keep a diary - record events for each day.
   - write important dates and times down prior to your first treatment and as you go along.
   - keep a calendar - mark off each day.
   - seek assistance with reorientating yourself.

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4. **Headache**
   Can be caused by the anaesthetic, by the treatment or by being without food for an extended period of time.

   Ways to relieve
   - have something to eat.
   - request pain medication before headache becomes too severe .
   - use relaxation tapes to help reduce muscle tension - ask your nurse where you may obtain these.
   - use distraction techniques, e.g. counting aloud. (ceiling tiles), imagery (imagine you are strolling in your favorite spot).
   - rest in a darkened room.
   - apply a cold cloth to your forehead.

5. **Nausea**
   Can be caused by the anaesthetic or by being without food or fluid for an extended period of time.

   Ways to relieve
   - eat small amounts of food, eg. soda crackers, dry toast.
   - rest.
   - request medication before nausea becomes too severe.

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Follow Up - What will happen after my ECT treatments?

Once you start feeling better, you will be discussing with your doctor and your nurse what can be done to maintain your improvement. Some of these suggested methods may include:

- Anti-depressant therapy (medication)
- Psychotherapy
- Maintenance ECT (This can be administered to you as an outpatient.)

NOTE:

You are welcome to continue with the ECT group after your treatments are finished (UBC Site).

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APPENDIX I

Why is ECT effective for Parkinson's Disease?

Drugs used for the treatment of Parkinson's Disease replace or mimic a missing brain chemical called "dopamine". Used carefully, these drugs work well for many years. However, over time, in certain patients, these dopamine agents can cause psychosis. Symptoms of this condition can include hallucinations or delusions (see page 2, "Who needs ECT?"). The psychosis can be treated by lowering or stopping the dopamine replacing drugs. This leads to a difficult choice as the patient's mobility depends on these drugs.

ECT is an effective treatment for this condition as the psychosis will clear, allowing patients to tolerate an adequate dose of the dopamine replacing drugs. How ECT works remains uncertain. For reasons that are also not understood, ECT can improve the symptoms of Parkinsons' Disease.

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Questions

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This pamphlet is intended to supplement the advice given by your doctor. There may be complications or instructions which are not listed. You should consult your doctor about any undesirable side-effects.

The information in this document is intended solely for the person to whom it was given by the health care team.

Developed by: Psychiatry Nursing & Education Services, University Hospital

Revised by: Marg Acton, Educator & Jeanette Eyre, ECT Coordinator
UBC Hospital

For more copies, contact H.R. - Education Support Services (875-4469)
and quote Catalogue No. **CD 270 EL25**

Chapter 4

TECHNIQUE, EQUIPMENT, AND EVALUATION

Setting

ECT can be provided in a variety of settings. For centres where ECT is provided for a large number of patients, a designated suite housing a receiving/waiting area, the procedure room, and a post-ECT recovery area for close patient observation would be ideal.

Alternatively, ECT is also commonly offered in pre-operative hospital holding areas, or within an operating room itself. Essential elements to any site include the provision of privacy for the patient receiving ECT, and adequate space for the anaesthetic and ECT equipment, as well as for staff to assist with the procedure. ECT should be carried out close to the necessary resources in case of a medical emergency.

In addition to the post-ECT room, patients undergoing outpatient ECT should have access to a supervised day room (i.e., the lounge of an inpatient psychiatric ward), where they can rest, read, or eat until they are ready to be discharged.

Patient Preparation

The patient should

- Have their initial weight recorded on the ECT Checklist.
- Be NPO. (See Chapter 9, "Anesthesia Guidelines," on oral intake.)
- Remove jewellery, hair accessories, contact lens, glasses, hearing aids, and dentures. Local policy can state whether glasses or dentures can be kept for transport.
- Receive pre-ECT medications (if ordered) and most routine a.m. medications 1 hour before ECT, with sips of water if oral.
- Void his or her bladder and bowels.
- Be wearing an incontinence pad if he or she has bladder or bowel instability.
- Have pre-ECT vital signs and, if diabetic, blood sugars recorded on the chart before each treatment.
- Have clean hair if at all possible.

The physician should be alerted to any change in medication and patient status if notable since the last treatment.

Psychotropic Medications during ECT

A careful review of medication is essential before starting a course of ECT. Existing medications for medical illness can usually be continued throughout the ECT course and given one hour before the ECT with sips of water, or after the treatment when the patient is fully awake. Diabetic patients should be given priority if several patients receive ECT on the same day. Insulin and hypoglycemic agents are usually given after the treatment. Medical consultations may be requested for patients with poorly-controlled blood sugars or with respiratory or cardiovascular illnesses.

Consideration should also be given whether to continue psychotropic medications throughout an ECT course. As a general rule, it is favourable to discontinue as many medications as possible to decrease the risk of delirium and minimize cognitive side effects. This is particularly applicable to those bearing anticholinergic effects.

On the other hand, in bipolar patients, it may be necessary to maintain mood stabilizers throughout the ECT course; for example, to reduce the risk of iatrogenically shifting a patient's depressed state into mania.

No substantial evidence currently exists to support that the combined use of ECT and medications improves the efficacy of ECT in symptom reduction.

Psychotropic Medications during ECT, continued

Antidepressant Medications

■ Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are commonly administered throughout the ECT course. Conflicting reports exist about the safety of this; some point towards a possible improved result when combined with ECT, some report no improved results, and others suggest both shortened seizure length and prolonged seizure length. Discontinuing SSRIs before ECT may be recommended for patients at higher risk of post-ECT delirium (i.e., those on multiple medications, the elderly, or those with co-existent dementia). If SSRIs are continued, the anesthetist should be informed and alerted to the possible risk of a prolonged seizure.

■ Monoamine Oxidase Inhibitors (MAOIs)

Selective MAOIs (e.g., moclobemide) are likely safe to continue, although little data exists on their effects.

Nonselective MAOIs (e.g., phenelzine, tranylcypromine) are also likely safe to continue. If hypotension occurs during the ECT, indirect-acting vasopressors should be avoided and neosynephrine used instead. In such a circumstance, an anesthesia consultation should be done before the first ECT.

■ Tricyclic Antidepressants (TCAs)

These are likely safe to continue. TCAs with stronger anticholinergic side effects (e.g., amitriptyline, imipramine, trimipramine, clomipramine) have increased risk of creating post-ECT confusion, and should be discontinued if possible.

■ Bupropion Hydrochloride

No data exists about the safety of bupropion (Wellbutrin) during ECT. Due to case reports of spontaneous seizures, it should likely be discontinued.

■ Others (e.g., Venlafaxine, Nefazodone, Trazodone)

No data exists.

Psychotropic Medications during ECT, continued

Mood Stabilizers

■ Lithium Carbonate

Controversy about the use of lithium during ECT centres on reports of increased risk for delirium, prolonged seizures, and possible decreased seizure thresholds. Generally lithium is well-tolerated at lower doses, and may have to be continued in patients with refractory mood disorders. Lithium should be held the night before and the morning of ECT and given post-ECT. Lithium carbonate levels should be done before ECT.

■ Anticonvulsant Agents (Carbamazepine, Valproic Acid, Gabapentin, Lamotrigine, Phenytoin, Topiramate)

Again, clear guidelines do not exist, but reports point towards decreased seizure time, higher seizure thresholds, and possible decreased efficacy of ECT for improving mood symptom when they are used concomitantly with ECT. They are generally well tolerated, however. If they are being used as mood stabilizers, doses should be held the night before and the morning of ECT.

■ Antipsychotic Agents

Traditional antipsychotics lower seizure threshold, but as with TCAs, may increase post-ECT delirium if they hold a stronger anticholinergic profile (e.g., chlorpromazine, thioridazine, methotrimeprazine, and fluphenazine).

Little information exists about the safety or efficacy of combining ECT with novel antipsychotics.

Reserpine has been associated with death when used during ECT and should therefore not be used.

■ Benzodiazepines

Benzodiazepines are commonly used in a variety of psychiatric illnesses, and have a major effect on ECT. They clearly increase seizure threshold. Many reports also define their role in lessening seizure efficacy for mood symptoms. If the indications for benzodiazepine use cannot be managed by other substitute agents (e.g., sedatives, antipsychotic agents), then

- Benzodiazepines with medium half-life (i.e. 8 hours) should be used, and held the morning of ECT.
- IV Flumazenil can be used in the treatment room if it is clear the benzodiazepine impacts upon ECT efficacy. IV Midazolam should then be given in the PAR room to ensure withdrawal symptoms do not occur.

Equipment

ECT Devices

Initial models of ECT devices (such as Med Craft) provided a sine wave stimulus. Advancing knowledge about the effects of different waveforms in ECT has resulted in the development of brief pulse devices. These offer an equally sufficient stimulus, but with notably less cognitive side effects. Given this key finding, brief pulse devices have become readily available and are in widespread use. (See the following chart.) Sine wave machines are no longer acceptable for modern ECT delivery.

Bi-Directional Brief Pulse Square Wave ECT Devices (North American Suppliers)

Supplier	Model	Pulse Width	Frequency	Duration	Current	Maximum Charge
MECTA Corporation	Spectrum 4000Q or 5000Q	0.5–2.0 msc	30–70 hz	0.5–6 sec	500–800 mA	576 mC
Somatics Incorporated	Thymatron System IV	0.25–1.4 msc	10–70 hz	0.14–8 sec	900 mA	504 mC

ECT Equipment

- Brief pulse ECT machine and backup: brief pulse and constant current with wide output range.
- Electrodes: flat and concave for unilateral placement.
- Patient stimulus cable, +/- hand-held paddles.
- EEG cable.
- EEG disposable electrode pads.
- EEG recording paper.
- Adjustable headband.
- Bite-blocks.
- Tube of electrode gel.
- Jar of abrasive conductant gel.
- Alcohol (for cleaning skin).
- 2 x 2-inch gauze (for cleaning skin).
- Bottle of buffered bleach (for cleaning equipment in MRSA-positive patients).

Skin Preparation

For electrical current from an ECT device to reach the brain, it must flow between two metallic electrodes. Since blood is a conductor, the brain's vascular system carries the current. Skin inherently resists electrical current, so careful site preparation is a key component in ECT delivery. Inadequate cleansing or sloppy use of conductant gel can result in an inadequate or aborted seizure, and in skin burns. Skin or scalp preparation involves

- Thoroughly cleansing the chosen electrode sites with alcohol-soaked gauze squares to remove oil, makeup, gel from previous treatments, hair sprays, dead skin cells, etc. Note that shaving the hair is not required. If a parietal site is used for unilateral ECT, hair can be parted and cleaned as described.
- Massaging an abrasive conductive such as that used in EEG labs into the skin with fingertips, in a circular motion.
- Removing the abrasive gel with a cloth or dry gauze (not with alcohol), to create a dry, clean, mildly-abraded area.
- Applying a conductive ECT gel (non abrasive), onto the electrode surfaces.
- Firmly pressing the electrodes against the skull, which is imperative to minimize impedance.

Electrode Placement

Electrode placement continues to be controversial and under active research and debate. It is generally accepted that bilateral placement is somewhat more effective than unilateral placement, but that the latter creates less cognitive side effects. Of interest is the emergence in the past few years of new electrode sites. Treating physicians should follow changing recommendations as they develop, and familiarize themselves with the benefits and detriments of the various options.

■ Unilateral Placement

The d'Elia position has become the recommended electrode placement site for unilateral, non-dominant hemispheric ECT:

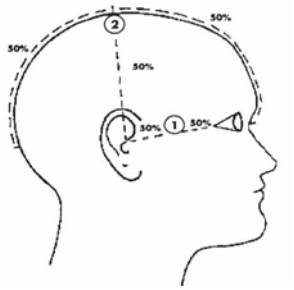

Figure 1: The midpoint of electrode one is placed one inch above the midpoint on an imaginary line drawn between the external canthus of the eye, and the tragus of the ear (i.e., the bottom edge of a two-inch electrode is on the line). The second electrode is similarly placed one inch on the right-hand side of two imaginary intersecting lines; the first drawn between the two tragi of the ears; the second connecting sagittally the inion with the nasion.

(From *The Practice of Electroconvulsive Therapy*, 2nd ed., p. 154[1].) www.appi.org Used with permission.

■ Bilateral Placement (Bitemporal)

The most widely used bilateral electrode placement has been bitemperofrontal. Electrodes are placed over both temples, as in Figure 1, Position 1, bilaterally.

Electrode Placement, continued

Other Positions

■ Bifrontal Placement

Bifrontal placement with electrodes close together appears to result in less clinical efficacy than the bitemperofrontal placements, albeit with less cognitive effects. Recent studies suggest two other bilateral strategies with wider bifrontal placements. The first is described in an original article, J.S. Lawson.[2] Alternatively, a Left Anterior Right Frontal position – the so-called "LART" is introduced by Schwarz.[3] Early work indicates that effective ECT may be deliverable closer to seizure threshold with bifrontal placement than with either bilatemporal or unilateral positioning.

■ LART (Left Anterior Right Frontal) Placement

The rationale for this electrode site option is that the left anterior electrode lies near the medial region of the frontal lobes, which is thought to be the cortical region most sensitive to seizure induction by electricity. It is also believed that one of the reasons these last two positions are more efficient in transmitting current is that these placements avoid skull sutures, and thereby avoid the concentration of electrical current as it enters the brain.
The end result is fewer cognitive side effects.

Stimulus Dose Strategies

Since the late 1980s, it has become apparent that the degree to which the electrical dose lies above seizure threshold has an impact on the efficacy of ECT. A stimulus delivered barely above seizure threshold can create a grand mal seizure, which will have little effect on improving target symptoms (i.e., depression). A stimulus that is markedly suprathreshold improves symptomatology, but also carries with it unnecessary cognitive side effects, causing patient suffering and a prolonged hospital stay.

From this have arisen differing approaches to dosing strategy. The "titration method" involves initially stimulating a patient with a very low electrical dose in "search" of threshold. Gradual dose increases are then delivered until an adequate seizure is obtained. "Adequacy" is determined via EEG morphology from the EEG readout delivered by the ECT device. From then on, the electrical dose for subsequent treatments is either maintained or gradually increased, using EEG criteria as well as clinical response as a guide. (See the following section, "Seizure Monitoring.")

Inherent to this method is the finding that seizure threshold varies from patient to patient. Concern exists that if all patients – regardless of age, gender, diagnosis, medications, or number of previous ECT treatments – received the same dose, with the same electrode placement, some patients (for example, those with high seizure thresholds) will receive sub-optimal treatments. Others with low thresholds will be left with excessive cognitive effects. Various protocols are available for the titration method dose scheduling. These are described by Beyer et al.[6]

Stimulus Dose Strategies, continued

Another approach uses a formula to guide dosage using the patient's age. Starting treatments with half the patient's age is recommended.[4] For example, if a patient is 60 years old, ECT is initiated at 30% of the maximum output deliverable by the device, then gradually the dose is increased as the ECT course progresses. Starting ECT at three-quarters of the patient's age is also possible.

Finally, some practitioners offer high, fixed-dose, right unilateral ECT for all patients.

Unresolved, and under active research, remains the effect of individual pulse morphology, which can be altered on some devices (MECTA SR II, JR II, Spectrum 5000Q, and Thymatron System IV).

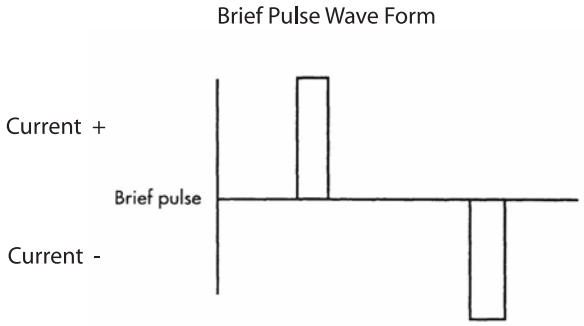

Figure 4: Brief Pulse Wave Form (From *The Practice of Electroconvulsive Therapy*, 2nd ed., p. 1401.) www.appi.org
Used with permission.

Shortened pulse width (0.5 msec or less) and longer pulse trains have now been linked with increased efficacy in research studies.

Debate also continues on the optimal dose of electricity above seizure threshold. Previously, 2.5 times threshold was considered adequate for unilateral ECT. Some authors[5] recommend 5 to 6 times threshold. However, this is technically not viable for many practitioners, given the maximum output deliverable by current devices; 1.5 to 2.5 times threshold for bilateral ECT (frontotemporal placement) is generally accepted.

Seizure Monitoring

Central to the delivery of safe and effective ECT is the assurance that

- A seizure has indeed occurred.
- The seizure is generalized to both hemispheres.
- The seizure is of adequate intensity to actually bring about symptom recovery.
- Unnecessary cognitive side effects are avoided.

Several parameters are observed to help with these clinical judgements:

EEG Activity

It was previously believed that seizure length in ECT reflected seizure adequacy; it was thought a seizure should be at least 25 seconds long in order to be effective. It is now clear that seizure time is less important than seizure intensity. Although many factors can affect seizure expression, current evidence suggests that the following are associated with better clinical outcomes

- Higher amplitude spike and wave activity.
- Sharp post-ictal suppression. (Numbers correspond to those in Figure 5 below.)

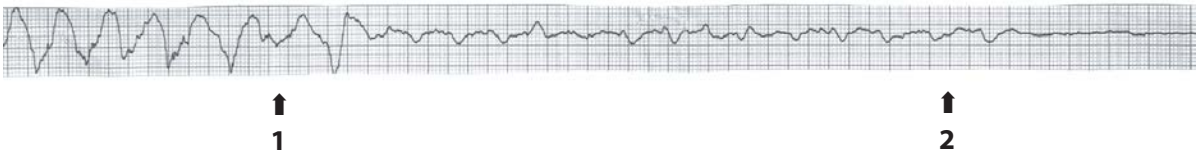

Figure 5: EEG Activity associated with better clinical outcomes. Used with permission of Dr. C. Gosselin

The current recommendations for EEG electrode placement sites are minimally one-channel (left side for right-unilateral ECT), but preferably two-channel frontal mastoid placement

- At the frontal site, 1 to 3 inches above the eyebrow on the mid pupillary line.
- At the mastoid site, over the hair-free mastoid bone, directly behind the ear.

Skin should be cleaned with alcohol, dried, +/– use of an abrasive gel for optimum recording. Pediatric disposable ECG electrodes work well.

Ictal motor activity (optional)

The motor component of a seizure can be monitored using the cuff method. The distal portion of a limb (preferably the ankle) can be blocked from receiving muscle relaxant by inflating a blood pressure cuff above the ankle to a pressure 100 mm Hg above the systolic pressure before ECT (i.e., 250 mm Hg). The cuff should be placed on the same side of the electrodes for unilateral ECT to ensure generalization. This technique is performed before the delivery of the muscle relaxant. The cuff should be deflated immediately following the seizure to avoid ischemia.

Seizure Monitoring, continued

The benefit of this method is evidence of a generalized seizure in the event of a faulty EEG. Limitations are that

- Tonic/clonic seizure activity stops before seizure activity ceases in the brain, i.e., motor component timing is not useful in measuring the true total seizure time.
- This technique is not appropriate for patients with skin or some musculoskeletal diseases such as severe osteoporosis, deep vein thrombosis, and sickle cell disease.

Cardiovascular Response

ECT affects the brain and the cardiovascular system. With the initial parasympathetic and then sympathetic outpouring that results from the seizure itself, brief but impressive falls and rises in blood pressure and heart rate occur. Continuous ECG monitoring as well as repeated blood pressures and oximetry before, during, and after the procedure are of vital importance.

Missed or Aborted Seizures

After a stimulus in ECT, it is possible that no seizure is elicited, or that a brief response (less than 15 seconds) results. It is unlikely that most patients can expect to benefit from a seizure of this short duration, although it is described that some inherently undergo brief seizures (e.g., 17 sec.), with nevertheless clear and progressive recovery. Possible causes of missed or aborted seizures are

- Excessive impedance from poor skin contact.
- Hypercarbia from inadequate ventilation.
- Hypoxia.
- Dehydration.
- Medications (typically benzodiazepines and anticonvulsants).
- Insufficient stimulus.

Possible remedies for missed or aborted seizures are to

- Review the "dynamic impedance" reading, which is elicited by the ECT device. If it is too high, examine and correct skin preparation, gel application, and/or electrode positioning.
- If not too high, restimulate at 50 – 100% above the original dose:
  - If a seizure is missed, wait 20 seconds before restimulating to ensure a delayed response will not occur (rare).
  - If a seizure is aborted, wait 45 seconds before restimulating to overcome the refractory period.
  - A third stimulus under the same anesthetic may be tried at a higher dose still, after another 45–second time lapse, and after it is ensured that no additional anesthetic and muscle relaxant needs to be given.
- Review the other factors above, such as correct hydration and electrolyte balance. Oxygenate adequately and ventilate vigorously prior to the next stimulus. If possible reduce or discontinue medications that may hinder the ECT, Flumazenil 0.5 to 1.0 mg iv can be used during the anesthetic for patients receiving high-dose benzodiazepines that cannot be altered. This can be followed by IV midazolam administration in the PAR to avoid withdrawal symptoms.
- Note that caffeine sodium benzoate, 500 to 2000 mg iv (or orally one-hour pre ECT with sips of water), can lengthen seizure time.

Prolonged Seizures

The APA ECT Task Force defines a prolonged seizure as greater than 180 seconds. The British Royal College of Psychiatrists defines it as 120 seconds. Prolonged seizures may lack a motor component; this is one of the most compelling arguments in favour of EEG monitoring in ECT. Possible remedies are to

- Abort the seizure with a benzodiazepine (diazepam, midazolam), or with an anticonvulsant anaesthetic agent (thiopental) intravenously.
- Intubate if necessary.

Evaluation of Individual Courses of Treatment

Before an index course of ECT treatment, each patient should have a treatment plan specifying criteria for remission. The patient's symptoms should be documented before a course of treatment in order to be able to assess progress in specific target symptoms during treatment. A baseline clinical global impression or the use of a rating scale like the Hamilton Rating Scale for Depression may be helpful.

Clinical assessment should be performed and documented by the attending physician before the course of ECT, and weekly during the course of ECT. If performed, cognitive assessments should be done at least 24 hours after the ECT treatment.

The total number of ECT treatments required by a patient should be guided by the patient's degree and rate of clinical improvement, and the development and severity of cognitive adverse effects. The frequency of ECT treatments should be guided by the severity of illness and the development and severity of adverse effects.

Evaluation of Individual Courses of Treatment, continued

Frequency and Number of Treatments

It is usual practice to do 2 or 3 ECT treatments per week, administered on non-consecutive days. In a major depression, a course of ECT usually consists of 6-12 treatments.

The use of daily treatments may be useful early in the treatment course when rapid response is important, such as mania, catatonia, high suicide risk, and severe inanition. With bilateral treatments, prolonged daily treatments increase the risk of cognitive impairment; the use of frequent treatment regimens has not been justified.

The use of multiple ECT (the delivery of more than one adequate seizure per treatment session) is not recommended.

For those patients who have improved with ECT treatments, the ECT treatment course should be ended or tapered as soon as it is evident that a maximum response has been attained.

If confusion or marked deterioration in cognitive functioning occurs associated with ECT, consider the following remedies

- Review potential medical and medication causes.
- Reduce treatment frequency (e.g., from 3 treatments per week to 1 – 2 treatments per week).
- Reduce the stimulus dose.
- Change electrode placement from bilateral to right unilateral.
- Suspend treatments until cognitive functioning improves.

If there is a slow or minimal clinical improvement after 6 – 10 treatments, the indication for continued ECT should be reassessed. If the decision is to continue with ECT treatments, consideration should be given to optimize ECT technique by

- Increasing the stimulus intensity.
- Changing from unilateral to bilateral electrode placement.
- Reducing or removing medication that may decrease response (e.g., benzodiazepines, anticonvulsants, propofol).

If repeated courses of ECT are necessary, the cognitive effects associated with prior treatment courses should be taken into consideration. If cognitive deficits are persistent and severe, a cumulative effect can occur with subsequent ECT treatments, especially with bilateral electrode placement.

It is recommended that after 15 ECT treatments, a formal reassessment be done, including a second opinion.

Evaluation of Individual Courses of Treatment, continued

Lack of Response to ECT

Patients should not be considered ECT failures or non-responders until they have had at least 10 treatments, and attempts have been made to optimize ECT response by

- Increasing the stimulus intensity.
- Changing electrode placement.
- Reducing or stopping medications that may effect response by effecting the seizure threshold (e.g., benzodiazepines, anticonvulsants, propofol).
- Changing medication strategies.

There are no clear strategies in treatment choices for ECT treatment non-responders. Some ECT practitioners try

- Psychotropic medication trials, different agents than before, or combinations.
- ECT and psychotropic medication.
- A different type of ECT: high-dose bilateral ECT treatment.

References

1. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001
2. Lawson JS, Inglis J, Delva NJ, Rodenburg M, Waldron JJ, Letemendia FJ. Electrode placement in ECT: cognitive effects. Psychological Medicine 1990; 20:335–344
3. Swartz CM. Asymmetric bilateral right frontotemporal left frontal stimulus electrode placement for electro convulsive therapy. Neuropsychobiology 1994; 29:174–178
4. Petrides G, Fink M. The "half-age" stimulation strategy for ECT dosing. Convulsive Therapy 1996; 12:138–146
5. Boylan LS, Haskett RF, Mulsant BH, Greenberg RM, Prudic J, Spicknall K, Lisanby SH, Sackeim HA. Determinants of seizure threshold in ECT: benzodiazepine use, anesthetic dosage, and other factors. Journal of Electroconvulsive Therapy 2000; 16:3–18
6. Beyer, J, Weiner, RD, Glenn, MD. Electroconvulsive Therapy: A Programmed Text, 2nd edition; APA, 1998

Chapter 5

MANAGEMENT OF ADVERSE EFFECTS

Postictal Delirium

Some patients develop postictal delirium following ECT. This is associated with marked agitation, disorientation, poor response to commands, and a sympathetic response. Bilateral electrode placement, high-intensity stimulation, and pre-existing cerebral impairment may increase risk for postictal delirium. It may take patients 5 - 45 minutes to recover. They are often amnesic for the episode. There is a risk of injury to the patient or staff due to marked agitation or thrashing. Depending on the severity of the symptoms, postictal delirium can be managed supportively, with reassurance or pharmacologically, with intravenous or intramuscular benzodiazepine agents (e.g., midazolam), or intravenous haloperidol.

If postictal delirium is recurrent or severe, it can be managed prophylactically with the use of the above agents after the onset of spontaneous respiration.

Cognitive Changes

The presence and severity of confusion and changes in cognitive functioning should be monitored during a course of ECT by reviewing nursing notes, bedside assessment of orientation and memory, and/or standardized testing such as the Folstein Mini-Mental Status Examination.

Assessment should be carried out before ECT and at least weekly throughout the index course. Cognitive assessment should be performed whenever possible at least 24 hours following an ECT treatment.

If there is a substantial deterioration of cognitive functioning during an ECT course, the physician administering ECT should

- Review the contributions of concomitant medications or the patient's medical status.
- Consider changing from bilateral electrode placement to right unilateral electrode placement during treatment.
- Consider decreasing the stimulus dosage.
- Change the interval between treatments; for example, if treatment frequency started at 3 times a week, decrease it to 1–2 times a week.
- Consider suspending a course of treatments.

If cognitive changes persist after completion of the course of ECT, a plan should be made for post-ECT follow-up, assessment and management.

Treatment Emergent Hypomania/Mania

A hypomanic or manic switch can occur during a course of ECT. In 1992, Angst and Angst[1] published a retrospective study of 1,057 hospital admissions between 1920 and 1981. They found that 12% of those diagnosed as endogenous depression and treated with ECT switched to hypomania. In the group diagnosed as psychotic depression, 10% switched to hypomania with ECT, and in the psychotic bipolar depressed patients, 32% switched to hypomania with ECT. The switch to mania or hypomania occurred more often in bipolar patients, or with patients with a family history of bipolar disorder.

There are no present established treatment guidelines for treating hypomanic or manic symptoms that occur following ECT treatments. Strategies can range from

- Stopping ECT and treating the manic symptoms with a mood stabilizer and/or antipsychotic.
- Suspending further treatments and observing the patient.
- Continuing ECT treatment to treat both the manic and depressive symptoms.

Delirium with euphoria, or "organic euphoria,"[2] can occur following ECT. This is characterized by confusion, disorientation and cognitive impairment. There is an associated silly, inappropriate quality to the patient's mood. This is usually a transient state lasting a few hours to days. Recovery can be facilitated by[4]

- Increasing the time between treatments.
- Decreasing the stimulus intensity.
- Changing from bilateral to unilateral electrode placement.

Other Adverse Effects

If there is any sudden onset of new risk factors, or worsening of the risk factors identified pre-ECT, these risk factors should be evaluated before the next ECT treatment. The patient's complaints concerning ECT should also be considered.

References

1. Angst J, Angst K, Baruffol I, Meinherz-Surbeck R. ECT-induced and drug-induced hypomania. Convulsive Therapy 1992; 8:179–185
2. Devanand DP, Sackeim HA, Decina P, Prudic J. The development of mania and organic euphoria during ECT. Journal of Clinical Psychiatry 1988; 49:69–71
3. Fink M, Kahn RI. Behavioral patterns in convulsive therapy. Archives of General Psychiatry 1961; 5:30–36
4. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001, Chapter 5.

Chapter 6

DOCUMENTATION OF INDIVIDUAL COURSES

Documentation of the Course of ECT

The Head of the Department of Psychiatry is responsible to ensure that there are policies in place to support adequate documentation of ECT. Documentation is an important aspect of ECT in order to provide the basis for continued assessment and reassessment of the patient's progress, and to provide a guide to effective treatment.

Documentation of the Course of ECT, continued

Before an Index ECT Course

The attending psychiatrist should document the following items in the patient's chart; the treating psychiatrist should confirm that they are documented

- Indications for ECT referral.
- Assessment of benefits and risks.
- Mental status, including target symptoms and base line cognitive functioning (e.g., Folstein Mini-Mental State Examination).
- Signed consent document.
- Charting recording the process of establishing informed consent.
- Appropriate physical evaluation within 10 days before starting an inpatient course of treatment, and 30 days before the start of an outpatient course of ECT.
- Pertinent laboratory investigations. Although there are no routine requirements for investigations, and investigations are patient- and hospital-specific, it is recommended that an EKG be done for patients over 45 years old.
- Consultation reports as indicated (anesthetic or medical).

Checklists are encouraged. The following examples appear at the end of this chapter

- UBC Mood Disorders Centre ECT Checklist (see Appendix A).
- Vancouver Hospital ECT Therapy Treatment Record (see Appendix B).
- Riverview Hospital Pre-ECT Medical Checklist (see Appendix C).
- St. Joseph's General Hospital ECT Checklist (see Appendix D).

Before a Maintenance Series of ECT

Before beginning a maintenance series of ECT, the treating psychiatrist should confirm that the patient's clinical record includes documentation of the following material

- Indications for maintenance ECT
- A signed consent form at least every 6 months or 15 treatments
- Charting of the elements of the informed consent process.

Documentation of the Course of ECT, continued

Between ECT Treatment Sessions (Index or Maintenance)

The attending physician should chart in the patient's clinical record at least weekly during an index ECT course. The charting should contain information about therapeutic response and adverse effects. Cognitive effects can be determined by reviewing the nursing notes, and through bedside assessment of orientation and/or memory, and/or autobiographical memory. The use of standardized testing such as the Folstein Mini-Mental State Examination can be helpful. Cognitive assessment should be done and recorded at baseline before ECT, and one week following the last ECT treatment in an index course. For maintenance, cognitive assessment should be done as a baseline prior to starting, and monthly thereafter.

There should also be communication between the attending and treating physicians. The forms at the end of this chapter are examples of what can be used

- Maintenance ECT Record (see Appendix E).
- Riverview Hospital ECT Progress Records (see Appendix F).

Using such forms, the attending physician can fax information back to the treating physician about the progress of the patient between ECT treatments and any development of adverse effects.

If 15 ECT treatments are exceeded in an index course of treatment, a second opinion should be documented on the chart justifying the provision of further treatment. With maintenance ECT, documentation of therapeutic response and cognitive effects should occur either before each treatment, or at least monthly, if the patient is stable and treatments occur more than twice per month.

Documentation of the Course of ECT, continued

At the Time of Each ECT Session

For each treatment session, at least the following information should be documented in the patient's clinical record

Pre-Treatment

- Baseline vital signs
- Medication, including dosage given before entering the treatment room.
- Any changes in risk factors, presence of adverse effects, or complications, should be noted in the chart before treatment.

Treatment

- Vital signs taken during treatment.
- Notes from the anesthetist describing the patient's condition while in the treatment.
- Medication given in the treatment, including dosage.
- Stimulus electrode placement (bilateral, right unilateral, left unilateral).
- Stimulus parameter settings for each stimulus.
- Seizure duration, noting whether motor or electroencephalographic, the quality of the EEG seizure, and the quality of suppression of the EEG seizure.
- Any adverse effects or complications that occur during treatment, and the steps taken to deal with them, charted by the treating psychiatrist.

Post-Treatment

- Vital signs post-treatment.
- Medication given post treatment, including dosage.
- Notes from the anesthetist describing the patient's condition in recovery.
- Notes from the recovery nurse, anesthetist, or treating psychiatrist documenting occurrence and management of any complications during recovery.
- The patient's condition on leaving the recovery area.

It is useful to keep a copy of treatment information for outpatients in the outpatient clinic treatment area, especially a copy of the consent, and data on electrode placement, stimulus parameters, seizure duration, anesthetic record, and adverse effects.

Documentation of the Course of ECT, continued

Following Completion of the Index ECT Course or Maintenance ECT Series

The attending physician should enter the following information in the clinical record

- A summary of overall therapeutic outcome and adverse effects experienced as a result of the ECT course or series, and the rationale for choice of endpoint
- A plan for post-ECT clinical management and any plans for follow-up of adverse effects.

The attending physician may find the form "Riverview Hospital ECT Outcome Evaluation" useful as an example, which appears at the end of this chapter. (See Appendix G.)

References

American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001.

Enns MW, Reiss JP. Electroconvulsive therapy. Canadian Journal of Psychiatry 1992; 37:671–686

List of Chapter 6 Appendices

Appendix A:
ECT Check List, which is revised from the UBC Mood Disorders original

Appendix B:
Electroconvulsive Therapy Treatment Record, Vancouver Hospital & Health Sciences Centre, Department of Psychiatry. (Two-sided form listed as Page 1 and Page 2 in this document.)

Appendix C:
Riverview Hospital Pre-ECT Medical Checklist.

Appendix D:
St. Joseph's General Hospital, Comox, British Columbia. Electroconvulsive Therapy Checklist.

Appendix E:
Maintenance ECT Record. This document was created for the Electroconvulsive Therapy Guidelines by Dr. M.L. Donnelly. (Two-sided form listed as Page 1 and Page 2 in this document.)

Appendix F:
Outpatient ECT Progress Record Riverview Hospital.

Appendix G:
ECT Outcome Evaluation Riverview Hospital.

All of these documents may be used where appropriate to be helpful, as long as the origins are cited.

ECT Checklist

NAME:_____ SEX:_____
DOB:_____PHN:_____
HOSPITAL_____

UBC MOOD DISORDERS ECT CHECKLIST (Revised)

PRIMARY DIAGNOSIS:
- ☐ Major Depressive Disorder
- ☐ Bipolar Disorder, Depressed
- ☐ Bipolar Disorder, Manic
- ☐ Schizophrenia
- ☐ Schizoaffective Disorder
- ☐ Parkinson's Disease
- ☐ Other (please specify):

INDICATIONS FOR ECT: (check all that apply)
- ☐ Rapid response needed
- ☐ Acute suicidality
- ☐ Physical deterioration
  - ☐ Refractory to medications
- ☐ Other (please specify):

PREVIOUS ECT RESPONSE: ☐ Not applicable ☐ Good response ☐ Limited or no response

PATIENT: ☐ Voluntary ➡➡ ☐ Risks/benefits explained ➡ ☐ Patient consent signed
STATUS: ☐ Involuntary ➡➡ ☐ Second opinion completed ➡ ☐ Medical director consent signed (± patient consent)

PRE-ECT WORKUP: ☐ Physical Examination ☐ Lab ☐ ECG (if necessary)
☐ Anaesthesia consult ☐ ECT orders written

OUTCOME MEASURES	**PRE-ECT**	**POST-ECT (at time of new consent for maintenance, either 6 months or 15 treatments)**
Folstein Mini-Mental State Exam		
Clinical Global Impression	☐ Not at all ill ☐ Borderline ill ☐ Mildly ill ☐ Moderately ill ☐ Markedly ill ☐ Severely ill ☐ Extremely ill	☐ Very much improved ☐ Much improved ☐ Minimally improved ☐ Not improved ☐ Worse
Hamilton Depression Rating Scale (optional)		
17-item		
7-item		
24-item total		
Beck Depression Inventory (optional)		
Geriatric Depression Scale		
or Other Depression Scale		

REASON ECT STOPPED: ☐ Maximum Benefit ☐ Adverse Effects ☐ Limited or no response

From UBC Mood Disorders Centre. Used with permission.

VANCOUVER HOSPITAL & HEALTH SCIENCES CENTRE
DEPARTMENT OF PSYCHIATRY

ELECTROCONVULSIVE THERAPY TREATMENT RECORD

TO BE COMPLETED BY PSYCHIATRIST

DATE ______ NURSING UNIT ______
MR. MISS MRS ______ UNIT NUMBER ______
SURNAME ______ GIVEN NAME ______
DOCTOR ______ [illegible]
SEX AGE

Psychiatric Diagnoses ______

______ 2nd Psychiatric Opinion Yes ☐ No ☐

Medical Diagnoses ______

______

Medications ______

______

Anaesthesia Classification ASA ______ Anaesthesia Consult Available Yes ☐ No ☐

History of Previous ECT ______

Allergies ______

PRETREATMENT CHECKLIST

Physical exam within preceeding 7 days recorded on chart	☐	ECG	☐	Consent - Patient	☐
CBC	☐	Mental Status Exam	☐	Consent - Family	☐
Electrolytes	☐	Videotape Orientation (optional)	☐	Consent - Medical Director	☐

OUTCOME EVALUATION

To be completed at the termination of the course of ECT.

Number of treatments administered in total ______ number bilateral ______ number unilateral ______

Date of first treatment ______ Date of last treatment ______

RESULTS

Complete recovery	☐	Moderate Improvement	☐	No Change	☐
Marked Improvement	☐	Some Improvement	☐	Worse	☐

WHY WERE THE TREATMENTS STOPPED?

Patient was fully recovered ☐ No improvement occurred after a normally therapeutic trial ☐ Patient refused further treatment ☐

☐ Complications (specify nature) ______

SIGNIFICANT ISSUES FOR FUTURE CONSIDERATION

______

______

______

______

Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist

Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist
Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist
Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist
Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist
Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist
Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist
Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist
Treatment # ______ Date: ______ Pretreatment B.P. ______ P. ______	Pre-Op Medication and Anaesthesia ______ Anaesthetist	ECT Treatment Record and Comments	Bilateral ☐ Unilateral Rt ☐ Left ☐ Seizure Time (in sec.) ______ ______ Psychiatrist

Clinical Indications:

Major Depression
- ☐ Delusion Depression
- ☐ Suicidal
- ☐ Dehydration/↓ intake
- ☐ Lack of response to meds
- ☐ Previous Positive Response

Schizophrenia
- ☐ Lack of response to meds
- ☐ Catatonic subtype
- ☐ Depressed mood
- ☐ Previous positive response

Mania
- ☐ Lack of response to meds
- ☐ Mixed state
- ☐ Delirious mania

Others
- ☐ Lack of response/intolerant of meds
- ☐ Mood disorder 2^{o} medical condition
- ☐ Psychosis 2^{o} medical condition
- ☐ Catatonia 2^{o} to medical condition
- ☐ NMS

Medical Diagnoses: _____

_____

_____

_____

Allergies: _____

_____

Anesthesia Consultation:
Anesthetic ASA Class: _____
Pre-ECT meds ordered by:
Anesthesiologist ☐ Yes ☐ No
Physician ☐ Yes ☐ No

Current medication: (attach copy of mar sheet)

YES
- ☐ Physical exam within 7 days and charted
- ☐ Mental Status Exam

	ORDERED	DATE OF TEST
CBC (within 30 days)	☐	_____
Electrolytes (within 30 days)	☐	_____
EKG within 7 days	☐	_____
Spinal X-ray as clinically indicated	☐	_____
Chest X-ray as clinically indicated	☐	_____

ECT previously given: ☐ Yes ☐ No
Most recent ECT record on chart ☐ Yes ☐ No
Response to previous ECT treatment: _____

_____

_____

_____

_____

Psychiatric opinion: 1 ☐ 2 ☐

... by Dr. _____ date: _____
... by Dr. _____ date: _____

INPATIENT: Involuntary ☐ Voluntary ☐

CONSENT:	Yes	No
- Given by patient	☐	☐
- Deemed (Mental Health Act)	☐	☐
- Involved Family consulted	☐	☐
- Involved Family agreed	☐	☐

OUTPATIENT CONSENT:
- Consent/given by patient ☐
- Incapable: arranged ☐
- C.L.A.S. notified TSDM ☐

CHARTING:
- Psychiatric History ☐
- Rationale for ECT ☐
- Current Assessment of Cognitive Functioning ☐
- Mood/psychosis/behavioural scales (as applicable) completed ☐
- Info provided to patient and/or family about ECT ☐

Doctors orders written?

Starting date: _____

Starting ECT
- Unilateral : Right ☐ Left ☐
- Bilateral : ☐

Physician: _____
Date: _____

RIVERVIEW HOSPITAL

PRE-ECT MEDICAL CHECKLIST

RVH 3725 - 06/01: SF-RVH-618

PATIENT IDENTIFICATION AREA

St. Joseph's
GENERAL HOSPITAL
COMOX, BRITISH COLUMBIA

ELECTROCONVULSIVE THERAPY CHECKLIST

Pre-ECT Workup

1. History and Physical Examination (within two weeks) ( )
2. Lab work
   - CBC ( )
   - Urinalysis ( )
   - BUN (patients over 65 only) ( )
   - ECG - Date: _____ ( )
3. Date of last chest x-ray (or spinal x-ray): _____

ECT Checklist

Date / Treatment	1st	2nd	3rd	4th	5th	6th
1. Consent	( )	( )	( )	( )	( )	( )
2. History & physical report present	( )	( )	( )	( )	( )	( )
3. NPO after midnight	( )	( )	( )	( )	( )	( )
4. Hospital attire (gown)	( )	( )	( )	( )	( )	( )
5. Dentures/Jewellery/hairpins - removed	( )	( )	( )	( )	( )	( )
6. Name Band on	( )	( )	( )	( )	( )	( )
7. Voided	( )	( )	( )	( )	( )	( )
8. T. _____ P. _____; R. _____; B.P. _____	( )	( )	( )	( )	( )	( )
9. Blue card on chart	( )	( )	( )	( )	( )	( )
10. ECT sheets/anaes/ - on chart	( )	( )	( )	( )	( )	( )
11. ECT cart up to PAR on evenings	( )	( )	( )	( )	( )	( )
Initial RN/RPN						

MAINTENANCE ECT RECORD

NAME:_____

DOB: _____ SEX:_____ AGE:_____

PHN: _____

			SYMPTOMS BEING MONITORED					
Date of Assessment	Date of Last ECT	# of Last ECT	Weight	Appetite	Energy Level	Mood	Comments Generally About Functioning	Name of Assessor
		1						
		2						
		3						
		4						
		5						
		6						
		7						
		8						
		9						

MAINTENANCE ECT RECORD

NAME:_____

DOB: _____ SEX:_____ AGE:_____

PHN: _____

			SYMPTOMS BEING MONITORED					
Date of Assessment	Date of Last ECT	# of Last ECT	Weight	Appetite	Energy Level	Mood	Comments Generally About Functioning	Name of Assessor
		10						
		11						
		12						
		13						
		14						
		15						

Created by Dr. M.L.Donnelly

Date: _____

Family Physician/Community Psychiatrist Report:

Caregiver Report:

Pre-ECT Nurse Assessment:

ECT Psychiatrist Assessment and Recommendations:

RIVERVIEW HOSPITAL

OUTPATIENT ECT PROGRESS RECORD

PATIENT IDENTIFICATION AREA

RVH : SF-RVH-

Clinical Indication(s): _____

Target Symptoms: _____

_____

_____

_____

ECT COURSE

Date of First Treatment: _____ Date of Last Treatment: _____ No. of Index Tx: _____

Bilateral: ☐ Unilateral: Right ☐ Left ☐ No. of Maintenance Tx: _____

Was electrode placement changed during course: Yes ☐ No ☐

Comments: _____

_____

_____

_____

OUTCOME OF ECT COURSE

If course completed:

Therapeutic outcome

- ☐ Patient improved. (Please provide copy of mood/psychosis/behavioural scales completed)
- ☐ No improvement
- ☐ Partial improvement (changes in scores)
- ☐ Effects on memory

Comments: _____

_____

_____

If course not completed:

- ☐ Patient refused further treatment
- ☐ Medical complications (explain) _____

_____

_____

_____

- ☐ Other (explain) _____

_____

_____

RECOMMENDATIONS FOR FUTURE ECT:

_____

Attending Physician's Signature

RIVERVIEW HOSPITAL

ECT OUTCOME EVALUATION

RVH 3782 - 05/01: SF-RVH-810

Original: Patient's Chart
Duplicate: To ECT Service

PATIENT IDENTIFICATION AREA

Chapter 7

CONTINUATION AND MAINTENANCE ECT

General Considerations

Traditionally when treating major depression, once remission of symptoms has been achieved, the 6-month period thereafter is described as the "continuation phase" of treatment, while treatment beyond the 6 months is classified as the "maintenance phase."[1] The continuation phase represents the period of particular vulnerability for re-emergence of symptoms, and pharmacotherapy is often recommended. In practice, it is difficult to distinguish between relapse (symptoms re-emerging during the continuation phase) and recurrence (symptoms re-emerging in the maintenance phase), thus this delineation may be less clinically useful.[2] This period of vulnerability may be longer in the elderly, ranging from 12 months[3] to 2 years.[2,4] Longer treatment for at least 2 years can also be appropriate for other vulnerable groups with major depression associated with chronic episodes, severe or life-threatening episodes, psychotic episodes, difficult to treat episodes, [3] episodes or greater, and frequent episodes (2 episodes or greater in 5 years).[2]

continued . . .

General Considerations

A number of studies have found high rates of relapse or recurrence in the 6- to 12-month period post-ECT, particularly without adequate continuation pharmacotherapy for depression.[5] Appropriate continuation pharmacotherapy can significantly reduce these rates. Continuation ECT (C-ECT), extending for the 6 to 12 months after acute ECT treatment, and maintenance ECT (M-ECT), extending beyond the C-ECT period, appear to be effective in preventing relapse and recurrence in all conditions with primary indications for use,[6] such as depression, mania, and schizophrenia. (See "Primary Indications for Use" in Chapter 3.) It can also be effective for Parkinson's disease.[7,8]

However, few prospective studies have compared C-ECT or M-ECT alone with pharmacotherapy. One recent study concluded ECT alone did not confer any advantage over continuation pharmacotherapy at 6 months in pre-ECT labelled "medication resistant" patients (50% relapse rate), but the comparison group was literature-based.[9] On the contrary, M-ECT combined with medication over one year for those with major depression or schizoaffective disorder conferred better outcome prospectively than pharmacotherapy alone.[10] Finally, a recent retrospective case controlled series yielded a similar beneficial result of C-ECT combined with medications.[11] This finding also appears to apply to an older group of patients (mean age 70) from an older, naturalistic study.[12] In conclusion, retrospective data and clinical experience strongly indicate there can be a clear benefit from C-ECT or M-ECT in certain cases; more prospective data are needed to confirm this observation.

Recommendations for Use

According to the APA Guidelines,[13] after a successful index course of ECT, continuation of ECT should be considered when

- Pharmacotherapy has been ineffective or unsafe in preventing relapse or recurrence.
- The patient (or substitute decision-maker) prefers to continue with ECT, and is willing to comply with the overall treatment plan, including behavioural restrictions associated with outpatient ECT.

Sparse data currently available indicate C-ECT or M-ECT combined with pharmacotherapy provides better outcomes than ECT or pharmacotherapy alone in selected patients. Further research, including the results of the ongoing 5-year NIMH-funded Consortium for Research in ECT (CORE), continuation ECT vs. pharmacotherapy prospective trial, will help clinicians decide whether single or combination treatment would be the most effective.

Some of those who remain well with C-ECT will benefit further from M-ECT. The duration of M-ECT to prevent recurrence is unclear, but there may not need to be a limited duration specified, or maximum number of M-ECT treatments, in those who particularly have "a strong history of recurrent illness, or when present or past attempts to stop or taper continuation treatment have been associated with return of symptoms."[13]

Process and Evaluation

C-ECT and M-ECT are typically given as outpatient treatments, ranging from weekly to monthly. Some will be maintained at less frequent intervals, such as every 6 to 8 weeks. Consent, technique, and evaluation, as covered in other chapters here, are issues to be tailored to the outpatient. It is suggested that

- The responsibility between the attending physician and ECT practitioner regarding who should monitor for target symptoms and cognitive function, and how consent should be obtained and renewed, should be clear for each case. In most instances, these would be the attending physician's responsibilities.
- The overall treatment plan should be reviewed and consent should be obtained at least every six months.[13]
- A register of patients undergoing ECT is helpful. A readily-accessible site where consents can be stored and brought up with each treatment is optimal.
- A discussion of the frequency of treatments and anticipated tapering schedule is strongly suggested before starting C-ECT. One tapering schedule suggests weekly ECTs for 1 month, biweekly ECTs for 2 months, and monthly ECTs for 3 months. Because of the vulnerability for relapse in the continuation phase of treatment, one might **not** need to taper ECT at such a prescribed frequency. Instead, the schedule of ECTs could be guided by each individual's clinical condition and his or her history of relapse when attempts have been made in the past to taper continuation treatment.

Special Considerations: Dementia and ECT

There may be some patients undergoing ECT (i.e., demented, brain injured, or minors) who may be incompetent to consent for C-ECT or M-ECT, but not commitable under the *Mental Health Act*. In these cases consent from a substitute decision-maker must be obtained, as set out in the *Health Care (Consent) and Care Facility (Admission) Act or the Mental Health Act*.

Of particular interest are those with co-existing dementia and depression, since there is considerable overlap in symptoms associated with the diagnosis of each. Disturbances in mood and affect seem to be more specific for mood disorder rather than motivational or vegetative symptoms.[14] Scales such as the Geriatric Depression Scale can aid in diagnosis in the presence of mild to moderate dementia,[15] particularly if there are reliable informants around. Complicating the issue further is that an index course of ECT may have a positive effect on general agitation in those with dementia,16 as well as benefiting those demented with major depression,[17] paralleling the efficacy of SSRIs for treating anxiety or some behavioural disorders associated with dementia.[18]

These factors should be taken into account before embarking on C-ECT or M-ECT in those patients with dementia. Clearly there will be those who attain a clear benefit in mood and affective symptoms, with improvement in function or social interaction. However, there will be those who become more placid due to less-specific effects of ECT, or due to a progression of dementia itself. Thus, finding alternative pharmacologic or non-pharmacologic maintenance treatments other than ECT would minimize risk of treatment in the long term. While C-ECT or M-ECT is considered a safe treatment in dementia, and there is no evidence for alterations of brain structure from contemporary ECT,[19] there are no data available to indicate whether M-ECT can or cannot adversely influence the cognitive deterioration in dementia. Therefore, for those with dementia, it is suggested that

- There must be significant benefit observed with an acute course of ECT before recommending C-ECT or M-ECT. There must be clear documentation of the indication for C-ECT or M-ECT, and the symptoms targeted.
- The risks and benefits of C-ECT or M-ECT are specifically discussed with the patient or the patient's substitute decision-maker, and documented.
- For those deemed to be incompetent to consent, a second psychiatric opinion is advisable, preferably from a geriatric psychiatrist, addressing both the clinical issues and the competency to consent issue.
- A review of the treatment plan and the need to continue ECT should be done every 6 months, including a re-evaluation of cognitive function and a discussion of this with the patient or the patient's substitute decision-maker.

References

1. Reesal RT, Lam RW. Clinical guidelines for the treatment of depressive disorders. II. Principles of management. Canadian Journal of Psychiatry 2001; 46 Suppl 1:21S–28S
2. Kennedy SH, Lam RW, Cohen NL, Ravindran AV. Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. Canadian Journal of Psychiatry 2001; 46 Suppl 1:38S–58S
3. Stoudemire A. Recurrence and relapse in geriatric depression: a review of risk factors and prophylactic treatment strategies. Journal of Neuropsychiatry and Clinical Neuroscience 1997; 9:208–221
4. Flint AJ, Rifat SL. The effect of treatment on the two-year course of late-life depression. British Journal of Psychiatry 1997; 170:268–272
5. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J. Continuation pharmacotherapy in the prevention of relapse following electro convulsive therapy: a randomized controlled trial. Journal of the American Medical Association 14-3-2001; 285:1299–1307
6. Rabheru K. The use of electroconvulsive therapy in special patient populations. Canadian Journal of Psychiatry 2001; 46:710–719
7. Wengel SP, Burke WJ, Pfeiffer RF, Roccaforte WH, Paige SR. Maintenance electroconvulsive therapy for intractable Parkinson's disease. American Journal of Geriatric Psychiatry 1998; 6:263–269
8. Aarsland D, Larsen JP, Waage O, Langeveld JH. Maintenance electroconvulsive therapy for Parkinson's disease. Convulsive Therapy 1997; 13:274–277
9. Wijkstra J, Nolen WA, Algra A, van Vliet IM, Kahn RS. Relapse prevention in major depressive disorder after successful ECT: a literature review and a naturalistic case series. Acta Psychiatrica Scandinavica 2000; 102:454–460
10. Swoboda E, Conca A, Konig P, Waanders R, Hansen M. Maintenance electroconvulsive therapy in affective and schizoaffective disorder. Neuropsychobiology 2001; 43:23–28
11. Gagne GG, Jr., Furman MJ, Carpenter LL, Price LH. Efficacy of continuation ECT and antidepressant drugs compared to long-term antidepressants alone in depressed patients. American Journal of Psychiatry 2000; 157:1960–1965
12. Vanelle JM, Loo H, Galinowski A, de Carvalho W, Bourdel MC, Brochier P, Bouvet O, Brochier T, Olie JP. Maintenance ECT in intractable manic-depressive disorders. Convulsive Therapy 1994; 10:195–205

References, continued

13. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001, Chapter 13:211.
14. Katz I. Diagnosis and treatment of depression in patients with Alzheimer's disease and other dementias. Journal of Clinical Psychiatry 1998; 59(Suppl 9):38–44.
15. Feher EP, Larrabee GJ, Crook TH. Factors attenuating the validity of the Geriatric Depression Scale in a dementia population. Journal of the American Geriatrics Society 1992; 40:906–909
16. Holmberg SK, Tariot P, Challapalli R. Efficacy of ECT for agitation in dementia: a case report. American Journal of Geriatric Psychiatry 1996; 4:330–334.
17. Rao V, Lyketsos CG. The benefits and risks of ECT for patients with primary dementia who also suffer from depression. International Journal of Geriatric Psychiatry 2000; 15:729–735
18. Raskind MA. The clinical interface of depression and dementia. Journal of Clinical Psychiatry 1998; 59 Suppl 10:9–12
19. Devanand DP, Dwork AJ, Hutchinson ER, Bolwig TG, Sackeim HA. Does ECT alter brain structure? American Journal of Psychiatry 1994; 151:957–970

Chapter 8

NURSING CONSIDERATIONS

Recommendations on Nursing Responsibilities

ECT is provided in a variety of settings in British Columbia hospitals. The following section outlines recommendations regarding nursing responsibilities in instances where the hospital in question has a designated suite for the delivery of ECT, and when the hospital delivers ECT in the OR, PAR, or ER.

Staffing for a designated ECT Suite

Treatment Coordinator

Qualifications

- RN/RPN with training in the use of ECT.

Responsibilities

- Book and schedule treatments.
- Contact outpatients to advise them of their treatment time.
- Provide education and support to outpatients and families as required.
- Assemble charts for outpatients.
- Ensure ECT equipment is available at the treatment area.
- Ensure treatment medications and emergency medications are available and current.
- Set up the treatment room.
- Assign designated nursing staff to specific roles during the treatment.
- Provide emergency interventions as required.
- Facilitate and organize orientation of new staff to ECT.
- Facilitate and organize in-service educational programs related to ECT.
- Develop guidelines for the nursing care of patients having ECT.
- Participate in the development of patient education materials.

Treatment/Recovery Room Nursing Staff

Qualifications

- RN with critical care training or at least recent medical-surgical experience.

Responsibilities

- Assist the treatment room coordinator in the treatment area as directed.
- Monitor patients in the post-anesthetic recovery room.
- Provide emergency interventions as necessary.
- Determine when to notify the anesthetist and/or the treating physician.
- Arrange for the patient's transfer back to the inpatient ward or for discharge when he or she is stable. (See the section "Pre- and Post-ECT Outpatient Nursing Care.")
- Provide reassurance and support to patients.

Staffing for ECTs Performed in the OR, PAR, or ER

Recommendations

- Ideally, designate a member of the nursing staff from the psychiatric unit as coordinator of the ECT program, and designate at least 2 members of the nursing staff in the treatment area to be responsible for the ECT treatments.
- Provide training for above staff members (according to training guidelines).
- Ensure designated staff is assigned to the treatment area.

Responsibilities

Psychiatric Unit Staff

- Provide education and support to patients and families.
- Ideally, accompany patients to the treatment area and remain with them until treatment begins.
- Attend the recovery area to assist with agitated patients as required.

See the section "Pre and Post-ECT Inpatient Nursing Care" for further details.

Staff in Pre-/Post-ECT Waiting Areas (Day Care Surgery)

See the section "Pre and Post-ECT Outpatient Nursing Care."

Coordinator of ECT Program

- Book and schedule treatments.
- Contact outpatients to inform them of their treatment time.
- Provide education and support to outpatients and families as required.
- Assemble charts for outpatients.
- Ensure ECT equipment is available at the treatment area.
- Facilitate and organize orientation of new staff to ECT.
- Facilitate and organize inservice educational programs related to ECT.
- Develop guidelines for the nursing care of patients having ECT.
- Participate in the development of patient education materials.

Staffing for ECTs Performed in the OR, PAR, or ER, continued

Treatment/Recovery Room Nursing Staff

- Set up the treatment area.
- Ensure treatment medications and emergency medications are available and current.
- Assist anesthetist/treating physician as necessary.
- Monitor patients in Post Anesthetic Recovery area.
- Provide emergency interventions as necessary.
- Determine when to notify the anesthetist and/or treating physician.
- Arrange for the patient's transfer back to inpatient ward or for discharge when he or she is stable.

Pre- and Post-ECT Outpatient Nursing Care

Goals of Nursing Care

The patient will

- Understand the need for having ECT, the possible side effects and the procedures to be carried out.
- Experience minimal physical side effects and psychological discomfort from ECT.
- Have his/her safety maintained before, during, and after ECT.

Interventions

Treatment Coordinator

When Referral for ECT Is Received

- Ensure the patient's clinical record is up-to-date and includes the following
  - Referral and booking forms.
  - Progress notes from the referring psychiatrist.
  - Current medication list.
  - ECT treatment records.
  - Nursing progress notes.
  - Current consent form.
- Assess and arrange for education required, including family members as necessary.

Pre- and Post-ECT Outpatient Nursing Care, continued

Interventions, continued

Staff in the Pre-/Post-Treatment Waiting Room

Pre-ECT

- Receive the patient in the designated area and ensure all necessary forms are with the chart.
- Collect baseline clinical data, including VS and mental status.
- Complete the ECT/Pre-Op checklist.
- Ensure prescribed pre-ECT medications have been taken.
- Ensure the patient has been NPO
  - for treatments given in the morning: from midnight
  - for treatments given later in day: according to hospital policy (no food for 5-6 hours, and only clear fluids up to 2 hours before the treatment).
- Assist the patient to change into hospital attire, according to hospital policy.
- Assess the patient's level of anxiety.
- Give the patient reassurance and support.
- When possible, ensure a staff member or responsible adult is available to remain with the patient before entering the treatment area.
- Ensure the patient voids before entering the treatment area.
- Assess the patient's potential for incontinence. Suggest wearing disposable briefs **only if necessary,** and with all geriatric patients.

Post-ECT

- Provide the patient with light breakfast/fluids.
- Give the patient reassurance and support.
- Assess the patient's vital signs and level of orientation before discharge.
- **Ensure that the patient is accompanied by a responsible adult when leaving** the treatment facility post-ECT, and will be escorted home.
- Instruct the patient and the accompanying adult regarding the need to
  - Be aware of possible side effects from the treatment or the anesthetic.
  - Report any untoward reactions to the attending physician.
- **Instruct the patient not to drive a vehicle for 24 hours.**
- Ensure the patient's personal effects go with him or her.

Pre- and Post-ECT Outpatient Nursing Care, continued

Staff in Treatment and Recovery Areas

See the section "Nursing Responsibilities in Treatment Areas."

Documentation

Complete ECT Nursing Record and Nursing Progress Notes, including any untoward events.

Pre- and Post-ECT Inpatient Nursing Care

Interventions

Pre-ECT

When ECT is ordered

- Assess the education required, including family members as necessary.
- Implement the education plan.
- Document the education carried out and its outcome.
- Ensure facility-appropriate chart forms are on patient's chart, including
  - The consent form..
  - Checklists.
  - Record of anesthesia.
  - Record of ECT.

The Day before ECT

- Assess the patient's physical and mental status.
- Commence the ECT/Pre-Op checklist.
- Encourage and/or assist the patient with personal hygiene, especially hair-washing.
- Encourage the patient to express concerns and feelings about his/her condition and ECT.
- Maintain NPO from midnight. **Remove *all* food and fluids from the bedside.**

Pre- and Post-ECT Inpatient Nursing Care, continued

Interventions, continued

The Morning of ECT

Complete the ECT/Pre-Op checklist.

- Confirm NPO has been maintained with the patient (according to outpatient guidelines).
- Assess the patient's potential for incontinence. Encourage the patient to void immediately before leaving ward. Suggest wearing disposable briefs **only if necessary**, and with all geriatric patients.
- Assess the patient's level of anxiety.
- Give the patient reassurance and support.
- When possible, accompany the patient to the treatment area.
- When possible, remain with the patient to provide support until he or she enters the treatment room

Post-ECT

On the patient's return to the ward

- Assess the patient's physical and mental status.
- Take the patient's blood pressure, pulse, and respirations within 5 min. of his or her return to the ward.
- Assess the frequency of observation required based on the patient's return to Pre-ECT vital signs and level of consciousness (e.g., q 15 min., q 30 min., q 1 hr).
- Assess the safety of the patient's environment and his or her readiness to ambulate and to swal low before giving morning medication and breakfast.
- Assess and document any side effects of the treatment.
- **Ensure the patient is accompanied when leaving the ward any time up to 24 hours post-ECT.**
- **Instruct the patient not to drive a motor vehicle for 24 hours post-ECT.**
- **Alert the patient's family and friends of the need for supervision for a minimum of 24 hours post-treatment.**

Documentation

Complete the following documentation

- Pre-treatment assessment data and interventions.
- Patient/family education, including their response to the education.
- Post-treatment assessment data and interventions.

Nursing Responsibilities in Treatment Areas

Nursing Care Goal

The patient will have safety maintained immediately before, during and following ECT.

Directives

A patient will be assessed for transfer/discharge from the recovery room post-ECT when

- The pre-and post-ECT scores correspond using a Post-Anesthetic Discharge Scoring System (see Appendix A). This form is part of the patient chart.
- The patient's vital signs are ±20% of baseline.

Inpatients

A recovery room nurse may transfer a patient to the unit of origin when the patient achieves the above patient specific discharge criteria. A physician will assess patients not meeting the discharge criteria in order for them to be transferred.

Outpatients

It is recommended that facilities providing outpatient ECT develop a policy statement and procedures that will address the discharge process of patients from the Post-Anesthetic Recovery room. Such a policy with corresponding procedures ought to include

- Criteria to be met before discharge (see above) using the discharge protocol form.
- Who may discharge the patient (e.g., a nurse certified to discharge the patient).
- Whom to call if a patient does not meet the discharge criteria.

A doctor's order for discharge is required if the above policy is not in place.

Interventions

The following interventions are suggested as guidelines and may vary according to hospital-specific policies, procedures, or practices.

In the Treatment Room

- Ensure all equipment is available (see Chapter 4, "Technique, Equipment, and Evaluation).
- Ensure that all required chart documentation is accurate and complete.
- Review the ECT checklist.
- Confirm that pre-ECT medications have been taken.
- Assist the patient onto the stretcher.
- Establish intravenous access according to the treating physician's order and facility practice.
- Pre-ECT, assess and record the patient's
  - Level of consciousness.
  - Respiratory status.
  - Muscle strength.
  - Skin color.

Nursing Responsibilities in Treatment Areas, continued

- Check and record BP and P pre-ECT.
- Cleanse electrode placement sites with alcohol swabs.

Interventions, continued

In the Treatment Room, continued

- Attach ECG and EEG electrodes.
- Attach the oximeter sensor.
- Record O_2 saturation on room air.
- Assist the anesthetist as required.
- Apply the BP cuff to limb as directed, and inflate 220 mm/hg before the injection of succinylcholine.
- Assist with the placement of ECT electrodes.
- Assist the treating physician with the treatment by holding the electrodes in place, and triggering the electrical stimulus.
- Apply gentle pressure on the patient's legs and arms to protect limbs from injury.
- Deflate BP cuff when the EEG has indicated seizure activity has stopped.
- Post seizure, record BP, pulse, and O_2 saturation.
- Remove the oximeter sensor, ECG leads, and EEG leads when directed.
- Assist in turning the patient to the post-anesthetic position.
- Assist with transferring the patient to the recovery room.

In the Recovery Room

- Prepare the recovery room for receiving patients post treatment
  - Check the wall suction and oxygen.
  - Check the pulse oximeter.
  - Test the patient monitoring system (if in PAR/ER).
- Receive a verbal report from the treatment room nurse and anesthetist.
- Commence 0_2 at 6–10 liters/min.
- Attach the oximeter.
- Check and record the patient's level of consciousness, respiratory status, muscle strength, and skin color
  - On admission.
  - Q5 minutes until it is equal to the pre-ECT score.
  - On discharge if more than 15 minutes have elapsed since the last recording.

Nursing Responsibilities in Treatment Areas, continued

Interventions, continued

In the Recovery Room, continued

- Check and record BP, P, and R
  - On admission.
  - Q5 minutes until vital signs are ±20% of baseline.
  - On discharge if more than 15 minutes have elapsed since the last recording.
- Check and record O_2 saturation
  - On admission.
  - Q5 minutes until $O_2 > 95$.
  - Before discharge if more than 15 minutes have elapsed since the last recording.
- Assist the patient to expel the artificial airway prn.
- Administer suction if required.
- Discontinue O_2 as indicated by the patient's condition, and check O_2 saturation on room air.
- Elevate the head of the stretcher.
- Check the patient's
  - Mouth and teeth for injury.
  - ECT electrode sites for redness and/or blistering.

Notify the physician and treatment room nurse if you note an injury, and complete an incident report as appropriate.

- Re-orient the patient to person, time, and place.
- Reassure the patient that treatment is over.
- Discontinue intravenous access.
- Notify the ward and accompanying adults that the patient is ready to be discharged from the recovery room.
- **Ensure the patient's personal effects go with him or her.**
- Give a verbal report to the ward nurse or, in the case of an outpatient, to the accompanying adult.

Documentation

Complete the ECT/PAR Nursing Record, including any untoward events.

References

American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001.

Chung, F. et al. A Post Anesthetic Discharge. Journal of Clinical Anesthesia, Vol 7, No 6, 1995, pp 500-506.

ECT—Pre and post nursing care. In Patient Care Guidelines. Vancouver, Vancouver Hospital and Health Sciences Centre, 2001.

ECT—Nursing responsibilities in the treatment and recovery rooms—Inpatients. In Patient Care Guidelines. Vancouver, Vancouver Hospital and Health Sciences Centre, 2001.

Glaser M. Criteria for discharge. In Frost EAM (editor). Post-Anesthetic Care Unit, 2nd Edition. Toronto, C.V. Mosby, 1990, pp63–72.

Halsall SM, et al. Nursing guidelines for ECT. In Freeman C (editor). The ECT Handbook. The Second Report of the Royal College of Psychiatrists' Special Committee on ECT. London, Royal College of Psychiatrists, 1995.

Kiadicki DM, Tackinow ML. Erasing the stigma of ECT. Journal of Post Anesthesia Nursing 1992; 7:84–88.

Russell E. Running an ECT department. In Advances in Psychiatric Treatment, Volume 7, 2001, pp57–64

NAME:_____ SEX:_____
DOB:_____PHN:_____
HOSPITAL_____

POST-ANESTHETIC DISCHARGE SCORING SYSTEM

SCORE	CRITERIA	ADM	POST ECT	5 MIN	5 MIN	DIS
Resp.						
2	Breathes deeply or coughs					
1	Dyspnea or limited breathing					
0	Apnea/Airway requires attention					
O2 Sat						
2	>95%					
1	90-95 %					
0	< 90%					
LOC						
2	Fully awake					
1	Arousable on calling					
0	No response					
Circ						
2	BP ± 20% preanaesthetic level					
1	BP ± 20-50% preanaesthetic level					
0	BP ± 50% preanaesthetic level					
Color						
2	Normal/Pink					
1	Pale, dusky, blotchy, jaundiced					
0	Cyanotic					
Strength						
2	Hand grasps strong					
1	Hand grasps weak					
0	No movement					
	TOTAL SCORE					

Chung, F. **Are Discharge Criteria Changing?** Journal of Clinical Anesthesia, Vol 7, No 6, 1995, pp 500-506.

Chapter 9

ANESTHESIA GUIDELINES

Requirements

All anesthesia providers must adhere to the *Guidelines to the Practice of Anesthesia* recommended by the Canadian Anesthesiologist's Society (revised edition 2000).[1] These guidelines address minimum requirements pertaining to

- the role of an anesthesiologist in patient care
- facility and equipment requirements in the anesthetizing location and recovery area.

Anesthetizing locations outside an accredited hospital operating room suite must follow the "British Columbia College of Physicians and Surgeons policy for non-hospital medical/surgical facilities."[2]

When anesthesia practitioners do not have the necessary equipment or staff's lack the necessary training or skills to safely and efficiently administer general anesthesia for electroconvulsive therapy and attend to the potential complications, or when the patient's medical condition dictates, a prudent practitioner should refer the patient to another practitioner or facility to provide optimal care.

Pre-Anesthetic Period

Anesthesia Consultation/Evaluation

An anesthesia consultation/evaluation should be requested before the first ECT, or during maintenance ECT when there is a significant change in the patient's medical status or medications. All patients with an ASA rating of 3 or above should have a consultation. The objectives of a consultation are to

- Determine the indication for ECT and any specific requirements that pertain to the proposed ECT therapy.
- Determine the history of anesthetic course during any prior ECT.
- Identify risk factors that may increase perioperative risk, and to take or suggest measures that would try to minimize that risk, including obtaining opinions from other consultants, laboratory, or investigative testing that may be deemed appropriate from the history and physical examination of the patient. Where risks are considered to be high, cancellation of the proposed procedure may be in the patient's best interests.

During the evaluation,

- A written report should be provided, documenting history and physical status, ASA classification, and specific concerns that may impact the proposed treatments and/or affect patient outcome.
- Pre-operative modification of antidepressant drugs should be discussed with the attending psychiatrist.
- Pre-operative orders to be administered before each treatment should be provided.

Pre-Operative Laboratory Testing

- No routine laboratory investigations are necessary; ordering of laboratory tests should be guided by the presence and severity of medical risk factors.
- It is suggested that practitioners follow the BC guidelines to electrocardiograms and pre-operative testing.[3]
- The potential for drug interaction and the autonomic instability that may manifest itself during ECT treatments should guide the clinician to consider obtaining baseline investigations that may not necessarily follow the BC guidelines to ECG and laboratory testing.
- Hospital or treatment facilities may define their own guidelines, depending on their specific circumstances.

Pre-Anesthetic Period, continued

Oral Intake

Minimum duration of fasting should be

- 8 hours after a meal that includes meat, fried, or fatty foods.
- 6 hours after a light meal (such as toast and a clear fluid).
- 2 hours after clear fluids.

If necessary, patients should be maintained on a level of observation sufficient to ensure compliance.

Should risk factors for aspiration be present, the anesthesiologist may elect to prolong the patient's NPO status, and pre-operatively prescribe a prokinetic agent such as metoclopramide, an H2 receptor blocker such as ranitidine, or a non-particulate antacid such as sodium citrate. This would be ordered in the pre-operative orders.

Patients at risk for relative dehydration should have an intravenous commenced early in the pre-operative period.

All diabetics should have a baseline glucometer reading performed. Thereafter, if indicated, a dextrose containing intravenous should be commenced.

Pre-Anesthetic Period, continued

Medications

Most regular medications should be continued during a course of ECT. They may be given with a sip of water the morning of treatment. (See "Psychotropic Medications during ECT" in Chapter 4.)

Physiological Changes During ECT

- Application of the electrical stimulus results in vagal stimulation regardless of whether a seizure is induced. The most apparent effect of this parasympathetic discharge is bradycardia. Asystole may occur, particularly in younger patients or individuals that have pre-existing cardiac conduction defects, or medications that affect conduction, such as beta-blockers.
- Seizure induction results in a sympathetic discharge with release of catecholamines and a resultant tachycardia and hypertension. The rate/pressure product increases dramatically; this may place the myocardium at risk for ischemia.
- Post seizure, baroreceptor-induced bradycardia may occur.
- During the seizure, cerebral blood flow increases markedly, oxygen extraction increases, and glucose metabolism increases.
- Cerebral autoregulation may be impeded, resulting in increased intracerebral pressure.
- Cardiac arrhythmias are frequent, but are usually self-limiting.
- Post-operative electrocardiographic changes showing ST-segment deviation and T wave inversion suggestive of subendocardial ischemia have been reported.
- Systolic performance of the left ventricle has been shown to be transiently impaired in patients not felt to be at risk for cardiac ischemia.
- Intraoccular and intragastric pressure increases.

The aforementioned physiological changes that may occur during ECT, coupled with the administration of anesthetic agents, is what places patients "at risk" for ECT. It is these factors that necessitate a complete evaluation of risk at the time of the anesthetic consultation. These risks must be balanced against those associated with medication use.

The Anesthetic Period

Unique Considerations

- Current ECT practice requires a general anesthetic.
- Neuromuscular blockade is necessary to attenuate the musculoskeletal manifestations of the seizure and to enable airway control and patency to permit ventilation and oxygenation.
- The selection of drugs and doses should be individualized to account for each patient's unique requirements.
- Potential drug interactions with antidepressants (e.g., MAOIs, lithium) must always be considered.
- Seizures persisting for more than 180 seconds should be considered prolonged, and should be terminated pharmacologically.

The protection of the teeth and oral structures requires special attention

- The electrical stimulus results in direct stimulation of the masseter, pterygoid, and temporalis muscles, causing an abrupt clenching of the jaw, despite muscle relaxation.
- A flexible bite-block should be used to distribute the force of the jaw contracting, to enable protection of the teeth and other oral structures.
- All patients, including edentulous patients, require a bite-block to be inserted.
- Partial dentures may remain in as a support to protect single or vulnerable teeth.
- The patient's chin should be supported to keep the jaw tight against the bite-block during the stimulus.
- A plastic airway (e.g., Guedel-type) should not be used as a bite-block.

The Anesthetic Period, continued

Procedure

- Perform equipment check, and ensure emergency drugs and apparatus are present, available, and functional.
- Ensure that stretcher is capable of Trendelenberg positioning.
- Review the patient's chart, including prior ECT anesthetic records.
- Ensure that the patient has an understanding of the proposed anesthetic.
- Discuss the planned procedure with the attending psychiatrist, including
  - Unilateral or bilateral electrode placement.
  - The necessity to titrate stimulus intensity.
  - The necessity to utilize proconvulsant drugs.
  - The requirement for limb isolation to observe motor manifestations of seizure.
  - The need for relative hyperventilation.
- Establish intravenous access via an indwelling canula.
- Ensure monitors are attached, and obtain a baseline recording of parameters.
- Administer anesthetic drugs, ensuring adequate pre-oxygenation, airway control, and placement of the bite-block.
- Administer intermittent positive pressure ventilation with 100% oxygen until the electrical stimulus, and continue post-stimulus until spontaneous and regular breathing are resumed.
- Ensure electrical isolation and support the mandible in occlusion before the stimulus.
- Ensure the patient's positioning is optimal to ensure his or her safety.
- When the patient is adequately anesthetized and haemodynamically stable, and muscle relaxation is optimized (90 seconds for succinylcholine), the ECT stimulus may be applied.
- During and immediately post stimulus, special attention must be directed to
  - Oxygenation and ventilation.
  - Hemodynamic stability. The blood pressure cuff should be cycled every 1–2 minutes. (A manual cuff may be required to record pressure, since the automatic cuff's cycle time and accuracy may be impeded by wide fluctuations in the blood pressure or by the presence of tachy or brady dysrrhymias).
- When the seizure has terminated, both in terms of motor and EEG evidence and hemodynamic stability is achieved, the patient may be placed in the lateral position to maintain airway patency.
- Once the patient is stable, rousable, and maintains spontaneous ventilation, he or she may be transferred to the recovery area. Oxygen should be administered by facemask during transit.
- The course of the anesthetic should be recorded.

The Anesthetic Period, continued

Anesthesia Drugs

The ideal induction agent would provide a short induction time that assured complete amnesia/unconsciousness throughout the period of muscle relaxation, including the seizure, while providing rapid titratability, hemodynamic stability, and a rapid recovery profile. It should have minimal to no effect on the seizure threshold, duration, or propagation of the seizure.

Methohexital

Methohexital was the most frequently-used induction agent for ECT, but is no longer available.

Sodium Thiopentone (Pentothal)

- Sodium thiopentone is the current drug of choice in some treatment facilities.
- This barbiturate increases the seizure threshold in a dose-dependent fashion.
- Repeat dosing may cause a prolonged recovery period.
- It is difficult to titrate to assure unconsciousness.

Propofol (Diprivan)

- A dose of 0.75 – 1.5 mg/kg results in a significant reduction of the magnitude of hemodynamic changes that accompany ECT.
- Propofol induces cerebral vasoconstriction, reduces cerebral blood flow and intracranial pressure, and decreases cerebral metabolic rate.
- Anticonvulsant action reduces seizure duration significantly.
- It is not shown to change therapeutic outcome compared to pentothal or methohexital.
- There is pain on injection, which can be reduced by injecting into a fast-running intravenous placed into a larger bore vessel. (Lidocaine should not be added to propofol, since it will increase the seizure threshold.)
- Propofol shows no benefit in the recovery profile compared to barbiturates (ECT use).

Muscle relaxants

- Muscle relaxants are used to minimize risk of a skeletal injury during seizure.
- Complete paralysis is neither desirable nor necessary, but should be tailored to the patient's need.
- A peripheral nerve stimulator allows a more accurate estimation of paralysis than clinical estimation.

The Anesthetic Period, continued

Succinylcholine

- Succinylcholine is the relaxant of choice in a dose of 0.5 – 1.0 mg/kg.
- Optimal relaxation occurs once all fasciculations have stopped.
- If a repeat dose be required, an anticholinergic agent should be given before the succinylcholine, to reduce the potential for asystole.
- Contraindicated in conditions with neurological deficit, malignant hyperthermia, hyperkalaemia, burns, atypical pseudocholinesterase, or cholinesterase inhibition.

Anticholinergic Agents

- Atropine in a dose of 0.3 – 0.6 mg iv. or glycopyrrolate 0.2 – 0.4 mg iv. may be used to decrease the bradycardia associated with the stimulus.
- Anticholinergic agents should be administered intravenously in sufficient time (1 – 3 minutes) before the stimulus to attenuate the vagal effects on the heart.
- They are recommended during the first treatment where the incidence of subconvulsive stimuli is higher while the convulsive threshold is evaluated.
- Glycopyrrolate may be a preferable drug in the elderly, since it is less likely to cause tachycardia and has a reduced incidence of postictal delirium compared to atropine.

The Anesthetic Period, continued

Post-Anesthetic Period

- Communicate any medical or anesthetic concerns to the recovery area nurse.
- Ensure the patient's airway, breathing, and circulation continues to remain stable, and administer supplemental oxygenation if required.
- Remain in the recovery area to receive the initial set of vital signs from the PAR nurse, including
  - Respiratory rate.
  - Pulse rate and rhythm.
  - Blood pressure.
  - Oxygen saturation.
  - Level of consciousness.
- Chart and sign anesthetic drugs and dosages PAR, noting comments regarding any complications and/or suggestions for changes for future ECT sessions on the anesthesia record.
- Either discard contaminated needles, syringes, and airway equipment in the appropriate containers, or send them to CSD for cleaning.
- Diagnose and treat abnormalities in vital signs and other complications, including, but not limited to
  - Postictal delirium.
  - Headache.
  - Nausea and vomiting.
  - Bronchospasm.
  - Angina.
  - Hypo/hyperglycemia in diabetic patients.
- Note serious complications in the chart and/or communicate them to the patient's physician.

The patient's medical condition is the anesthetist's responsibility until the patient is discharged from the PAR. Discharge from the PAR is a responsibility of the anesthetist, delegated to the PAR nurses who use established discharge criteria according to the "ECT Nursing Record." To be discharged from the PAR, the patient must be free of complications and have his or her vital signs returned to baseline.

References

1. Guidelines to the Practice of Anesthesia, Revised edition. Canadian Anesthesiologist's Society, 2000.
2. College of Physicians and Surgeons of British Columbia. Policy Manual Part XV. January 31, 2001.
3. Guidelines and Protocols Advisory Committee, BC Medical Services Commission. Electrocardiograms, April 2000; Routine Pre-Operative Testing, September 2000.
4. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures: American Society of Anesthesiologists, 1999.
5. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001.
6. Freeman C (editor). The ECT Handbook. The Second Report of the Royal College of Psychiatrists' Special Committee on ECT. London, Royal College of Psychiatrists, 1995.
7. Clinical Memorandum #12. Electroconvulsive Therapy, Revised. Royal Australian and New Zealand College of Psychiatrists, 1999.
8. ECT Manual. State of Victoria, Australia, 2000.
9. Miller ED, Miller RD (editors). Anesthesia, 5th Edition. New York, Churchill Livingston, 1999.
10. Kelly KG, Zisselman M. Update on electroconvulsive therapy (ECT) in older adults. Journal of the American Geriatrics Society 2000; 48:560–566.

Chapter 10

TRAINING AND PRIVILEGING FOR HEALTH CARE PROFESSIONALS

Introduction

The goal of training and privileging systems is to ensure that practitioners possess the knowledge and skills required to provide safe and effective treatment. This is even more important in the case of ECT, given the controversy and negative perceptions that surround ECT.

It is the responsibility of the authority providing the ECT service (usually a health authority) to ensure that professionals who provide the services have the necessary knowledge, skills and attitudes to provide safe and effective treatment in an environment that is empathetic to the needs of patients and their significant others. "Privileging" is the process where the chief of psychiatry or medicine assesses the knowledge and skills of a medical practitioner who wishes to be involved with the ECT treatment team, and decides to grant that privilege to the practitioner. A similar process should occur with nurses involved in ECT, where the director of nursing or other nursing authority ensures that the nurses working in the ECT service have the necessary knowledge, skills and attitudes, although this may not be formally known as "privileging".

Introduction, continued

In addition to professionals involved in direct administration of ECT who should go through a formal privileging system or its equivalent, a number of others need competence in aspects of ECT. For example, psychiatrists or general practitioners who prescribe ECT but do not provide it, and nurses on units where people receive ECT, need considerable knowledge about its indications, effects, side effects, patient education issues, and the like. While the health authority does not need a special ECT privileging system for these people, it does have a responsibility to ensure that professionals are competent and keep up with developments in the field.

Privileging and training are closely linked. Basic training is received before entering practice and subsequently is the basis for developing and maintaining the knowledge, skills, and attitudes that privileging requires. While the health authority is not responsible for preparing students in nursing and psychiatry, their feedback to professional schools in areas such as the delivery of ECT may be helpful for preparing students. In addition, health authorities along with the professions have a responsibility for ensuring that practitioners keep up-to-date on developments in ECT. This chapter includes lists of the knowledge and skills that should be considered in establishing privileging criteria for ECT.

Competencies Required

ECT has evolved into a complex medical procedure that requires interaction among many health care providers. To accomplish the successful outcome of electroconvulsive therapy, it is necessary for entire teams to stay abreast of the advances in the practice of ECT. This includes referring physicians, attending nurses, and staff of the ECT service, including staff in the receiving area, treatment area, post-operative recovery area, and the outpatient post-discharge area. Staff should be trained in the historic aspects of ECT as well as advances in technique, including stimulus dosing, electrode placement choices, physiological modifications of induced seizures, and physiological monitoring during ECT and in the recovery area, as well as post-ECT care on the ward or in outpatient clinics.

Physicians who do ECT need to have mastered the following knowledge levels or compentencies

- Indications for the use of ECT.
- Risk-benefit assessments.
- Patient selection and evaluation.
- Consent procedures for both voluntary and involuntary patients.
- Preparation of patients.
- Types and use of ECT equipment.
- Techniques of ECT administration.
- Anesthetics and muscle relaxants.
- Airway management and oxygenation.
- Bite-blocks and nerve stimulators.
- Electrode placement.
- Stimulus parameters and dosing, including the concept of threshold.
- Monitoring of EEG and motor convulsions.
- Electrophysiological monitoring of heart rhythms and blood pressure.
- Management of missed and prolonged seizures.
- The concept of inadequate seizure.
- Emergency use of ECT.
- Management of medical emergencies during ECT.
- Documentation of inter-ECT interval progress.
- Evaluation of therapeutic outcomes and side effects, in particular, cognition.
- The use of maintenance ECT.
- Post-ECT medication management, particularly to prevent relapse and recurrence.

Competencies Required, continued

Family physicians and psychiatrists referring patients for treatment need to know

- Indications for the use of ECT.
- Risk benefit assessments.
- Patient selection and evaluation.
- Consent procedures for both voluntary and involuntary patients.
- Documentation of inter ECT interval progress.
- Evaluation of therapeutic outcomes and side effects, in particular cognition.
- Post-ECT medication management, particularly to prevent relapse and recurrence.

To address recruitment and continuing education issues in remote or rural hospitals, a customized locaL continuing education program for interested physicians should be considered. The continuing education course should not only bring the knowledge and practice to contemporary standards, but should help form linkages with major teaching hospitals. Policies should be developed to refer patients to teaching hospitals if problems are encountered in the treatment process.

Continuing education programs should include both didactic lecture or seminar components and practical hands-on training with a mentor.

Privileging Physicians

The head of the department of psychiatry (or equivalent) should be responsible for privileging functions, including appointments, re-appointments, monitoring, performance appraisals, and recommendations for privileges to practice ECT. Privileges for ECT practice should be reviewed every second year.

It is recommended that privileges for the administration of ECT should be restricted to Royal College certified psychiatrists trained in ECT practice, whenever possible. Where trained psychiatrists are not available, another physician with an interest in psychiatry could be specifically trained in the modern practice of ECT to meet regional needs. In situations where the treating practitioner is a trained physician other than a psychiatrist, a mandatory psychiatric consultation should be required for every patient before ECT commences.

In determining whether a psychiatrist should be privileged for the ECT service the person responsible should use as a basis this Guideline including skills and knowledge outlined in this chapter, although it is difficult to get an agreement about what constitutes a basic minimum requirement for the practice of ECT and for the maintenance of competence. It is, however, recommended, that ECT practitioners must keep up with developments in the field in terms of research, advances in technique, and evolving indications for the use of ECT, as well as maintaining an active ECT practice on an bi-annual basis.

Training Nurses

Nurses play an important role in the delivery of electroconvulsive therapy, from patient and family education and preparation before treatment to follow-up and support for patients and family after treatment is given. Education about ECT needs to be included as part of basic nursing education. For those nurses entering the field of psychiatry, more extensive education needs to be provided. The following recommendations for training and orientation are intended to provide guidelines for schools of nursing and for hospitals providing psychiatric treatment.

Health Authority

General Nursing Staff
Nursing orientation should include an overview of ECT, including its history, indications, and potential risks.

Nursing Staff Working in Psychiatry and in Treatment Areas and Recovery Rooms
Nursing orientation in Psychiatry should include

- The history of ECT.
- Indications for and potential risks of ECT.
- Pre-ECT evaluation and medical review.
- Informed consent procedures.
- ECT technique.
- Information to be included in patient and family education.

In addition, nursing staff working in treatment areas and recovery rooms should have orientation, which includes nursing participation in ECT treatment and post-anesthetic recovery (including management of emergency situations).

Appointing Nurses

Ensuring Qualified Nursing Support
Management for mental health acute care services within health authorities should ensure job descriptions and qualifications, hiring processes and orientation are developed to ensure effective and supportive nursing care for patients receiving ECT services (see Chapter 8, "Nursing considerations"). Nurses require ongoing orientation sufficient to provide care that is based on current best evidence. Program and individual evaluations are provided to support nurses to achieve nursing practice standards and to implement changes when required.

References

1. Enns MW, Reiss JP. Electroconvulsive therapy. Canadian Journal of Psychiatry 1992; 37:671–686
2. Freeman C (editor). The ECT Handbook. The Second Report of the Royal College of Psychiatrists' Special Committee on ECT. London, Royal College of Psychiatrists, 1995.
3. Geagea, Justin . APA Annual Meeting, New Orleans, May 2001. Medical Post, Volume 37, No. 20.
4. American Psychiatric Association Task Force on Electroconvulsive Therapy. The Practice of Electroconvulsive Therapy. 2nd edition. Washington, DC, American Psychiatric Press, 2001

Chapter 11

QUALITY ASSESSMENT

It is recommended that each hospital providing ECT appoint an ECT Director to oversee the effective provision of ECT at that hospital, including

- the availability of patient and family education materials
- appropriate clinical care of patients
- monitoring of ECT as a therapy
- privileging of physicians to perform ECT.

Program Quality Improvement (QI Initiatives)

The purpose of quality assurance or improvement programs is to improve outcomes. It is only by critically looking at our work that we may objectively identify areas for possible improvements. Improved outcomes include

- Better staff training.
- Better information being received by patients, families, and other decision-makers.
- Reduction in side effects.
- Improved patient satisfaction.
- Improved patient outcomes regarding symptom reduction.

Monitoring of ECT should be the responsibility of the health authority, through quality improvement initiatives defined by designated psychiatric quality improvement teams. The following are recommendations for activities for quality assurance and/or improvement.

- As part of a QI process, an annual review should include one or more of the following
  - Documented consent.
  - Pre-ECT checklists.
  - ECT treatment forms.
  - Side effects and complications.
  - Basic treatment outcomes.
  - Patient and family education activities.
- A review of nursing and physician training, as well as privileging of ECT, should occur every second year.

Information to Be Kept by Health Authorities (HA)

The following information is considered essential for HAs to maintain, in order to understand their own appropriate use of ECT as a therapy, and for potential inter-hospital comparisons by the Ministry of Health Services. There should be a record of the following variables for each individual patient

- Age.
- Sex.
- Personal Health Number.
- Whether this is an index course or maintenance course of ECT.
- Whether this is an inpatient or outpatient.
- Dates of treatment.
- Names of the attending physicians and their professional degrees (family physicians or psychiatrists).
- Any side effects or complications that occurred during the course of ECT.
- The primary diagnosis as a reason for requiring ECT.
- The indications for ECT.
- A statement about previous ECT response.
- Whether the patient was voluntary or involuntary.
- Elements of pre-ECT workup completed.
- Basic outcome measures, including a cognitive scale, the clinical Global Impression Scale, a depression scale, and a patient satisfaction measure (qualitative or quantitative).
- The reason ECT is stopped.
- The number of unilateral and bilateral treatments.
- Treatment location (name of hospital).

Information to Be Kept by Health Authorities (HA), continued

Appendices A–D at the end of this chapter show sample forms and slightly-revised checklists from the UBC Mood Disorders Centre for index and maintenance courses of ECT.

Having maintained these individual records, Health Authorities should be able to collate the following data for inter-unit and inter-regional comparisons when required

- The number of inpatients and outpatients per year having an index course of ECT.
- The number of patients having maintenance ECT each year on an inpatient or outpatient basis.
- The age range and distribution of ECT treatment by sex.
- The average number of treatments for an index episode.
- The average number of treatments per year, per person, for maintenance ECT.
- A list of the primary diagnosis of the patients undergoing ECT.
- A list of complications related to ECT.
- Basic outcome measures.
- Reasons for stopping ECT.

Sample Form for Index Course of ECT

NAME:_____ SEX:_____
DOB:_____PHN:_____
HOSPITAL_____

INDIVIDUAL ECT RECORD: INDEX COURSE: COMPLETED ON DISCHARGE
Inpatient ☐ or Outpatient ☐

Dates of Treatments:	(+ Bil/Uni)	Dates of Treatments:	(+ Bil/Uni)
1._____	_____	9._____	_____
2._____	_____	10._____	_____
3._____	_____	11._____	_____
4._____	_____	12._____	_____
5._____	_____	13._____	_____
6._____	_____	14._____	_____
7._____	_____	15._____	_____
8._____	_____	Total Unilateral_____	Total Bilateral_____

Name of Physicians Monitoring Effects of ECT (Attending) — Professional Degree (Family Phys./Psych.)

_____ _____
_____ _____
_____ _____

Adverse Reactions and Complications:

_____
_____
_____
_____
_____
_____
_____

REASON ECT STOPPED: ☐ Maximum benefit ☐ Adverse effects ☐ Limited or no response

From UBC Mood Disorders Centre. Used with permission.

Sample Checklist, Index Course

NAME:_____ SEX:_____
DOB:_____PHN:_____
HOSPITAL_____

UBC MOOD DISORDERS ECT CHECKLIST (Revised)

PRIMARY DIAGNOSIS:
- ☐ Major Depressive Disorder
- ☐ Bipolar Disorder, Depressed
- ☐ Bipolar Disorder, Manic
- ☐ Schizophrenia
- ☐ Schizoaffective Disorder
- ☐ Parkinson's Disease
- ☐ Other (please specify):

INDICATIONS FOR ECT: (check all that apply)
- ☐ Rapid response needed
- ☐ Acute suicidality
- ☐ Physical deterioration
- ☐ Refractory to medications
- ☐ Other (please specify):

PREVIOUS ECT RESPONSE: ☐ Not applicable ☐ Good response ☐ Limited or no response

PATIENT: ☐ Voluntary ➡➡ ☐ Risks/benefits explained ➡ ☐ Patient consent signed

STATUS: ☐ Involuntary ➡➡ ☐ Second opinion completed ➡ ☐ Medical director consent signed (± patient consent)

PRE-ECT WORKUP: ☐ Physical Examination ☐ Lab ☐ ECG (if necessary) ☐ Anaesthesia consult ☐ ECT orders written

OUTCOME MEASURES	**PRE-ECT**	**POST-ECT (at discharge or one week post-discharge, or 15 treatments of maintenance)**
Clinical Global Impression	☐ Not at all ill ☐ Borderline ill ☐ Mildly ill ☐ Moderately ill ☐ Markedly ill ☐ Severely ill ☐ Extremely ill	☐ Very much improved ☐ Much improved ☐ Minimally improved ☐ Not improved ☐ Worse
Hamilton Depression Rating Scale (optional)		
17-item		
7-item		
24-item total		
Beck Depression Inventory (optional)		
Geriatric Depression Scale or Other Depression Scale		

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Sample Form for Maintenance Course of ECT

NAME:_____ SEX:_____
DOB:_____PHN:_____
HOSPITAL_____

INDIVIDUAL ECT RECORD: MAINTENANCE COURSE

Inpatient ☐ or Outpatient ☐

Dates of Treatments:	(+ Bil/Uni)	Dates of Treatments:	(+ Bil/Uni)
1._____	_____	9._____	_____
2._____	_____	10._____	_____
3._____	_____	11._____	_____
4._____	_____	12._____	_____
5._____	_____	13._____	_____
6._____	_____	14._____	_____
7._____	_____	15._____	_____
8._____	_____	Total Unilateral_____	Total Bilateral_____

Name of Physicians Monitoring Effects of ECT (Attending)	Professional Degree (Family Phys./Psych.)
_____	_____
_____	_____
_____	_____

Adverse Reactions and Complications:

_____
_____
_____
_____
_____
_____

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Sample Checklist, Maintenance Course

NAME:_____ SEX:_____
DOB:_____PHN:_____
HOSPITAL_____

UBC MOOD DISORDERS ECT CHECKLIST (Revised)

PRIMARY DIAGNOSIS:
- ☐ Major Depressive Disorder
- ☐ Bipolar Disorder, Depressed
- ☐ Bipolar Disorder, Manic
- ☐ Schizophrenia
- ☐ Schizoaffective Disorder
- ☐ Parkinson's Disease
- ☐ Other (please specify):

INDICATIONS FOR ECT: (check all that apply)
- ☐ Past failure on medications
- ☐ Past history of response to maintenance ECT
- ☐ Other (please specify):

PREVIOUS ECT RESPONSE: ☐ Not applicable ☐ Good response ☐ Limited or no response

PATIENT: ☐ Voluntary ➡➡ ☐ Risks/benefits explained ➡ ☐ Patient consent signed

STATUS: ☐ Involuntary ➡➡ ☐ Second opinion completed ➡ ☐ Medical director consent signed (± patient consent)

OUTCOME MEASURES	**PRE-ECT**	**POST-ECT (at time of new consent for maintenance, either 6 months or 15 treatments)**
Folstein Mini-Mental State Exam		
Clinical Global Impression	☐ Not at all ill ☐ Borderline ill ☐ Mildly ill ☐ Moderately ill ☐ Markedly ill ☐ Severely ill ☐ Extremely ill	☐ Very much improved ☐ Much improved ☐ Minimally improved ☐ Not improved ☐ Worse
Hamilton Depression Rating Scale (optional)		
17-item		
7-item		
24-item total		
Beck Depression Inventory (optional)		
Geriatric Depression Scale or Other Depression Scale		

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Feedback: Electroconvulsive Therapy

Guidelines for Health Authorities in British Columbia.

August 2002

The Electroconvulsive Therapy: Guidelines for Health Authorities in British Columbia document will be periodically updated. To assist in this process, please answer any or all of the following questions and send it to the address shown at the bottom of this form.

Thank you for your assistance.

1. Is this a useful document? Will it assist you in planning, delivering and evaluating Electroconvulsive Therapy in your region Briefly explain your response.

2. Please identify errors and identify any additional issues you would suggest for the next edition.

3. Does the document as a whole provide clear and appropriate guidelines for developing or improving ECT services?

Feedback: Electroconvulsive Therapy

4. Are the suggestions for data elements to be kept for Quality Improvement (QI) Purposes (on page?) complete? Do you have any concerns about being able to collect and analyse this data?

5. Additional comments: (Please attach another page if you need more space.)

Name _____

Position _____

Health Authority _____

Address _____

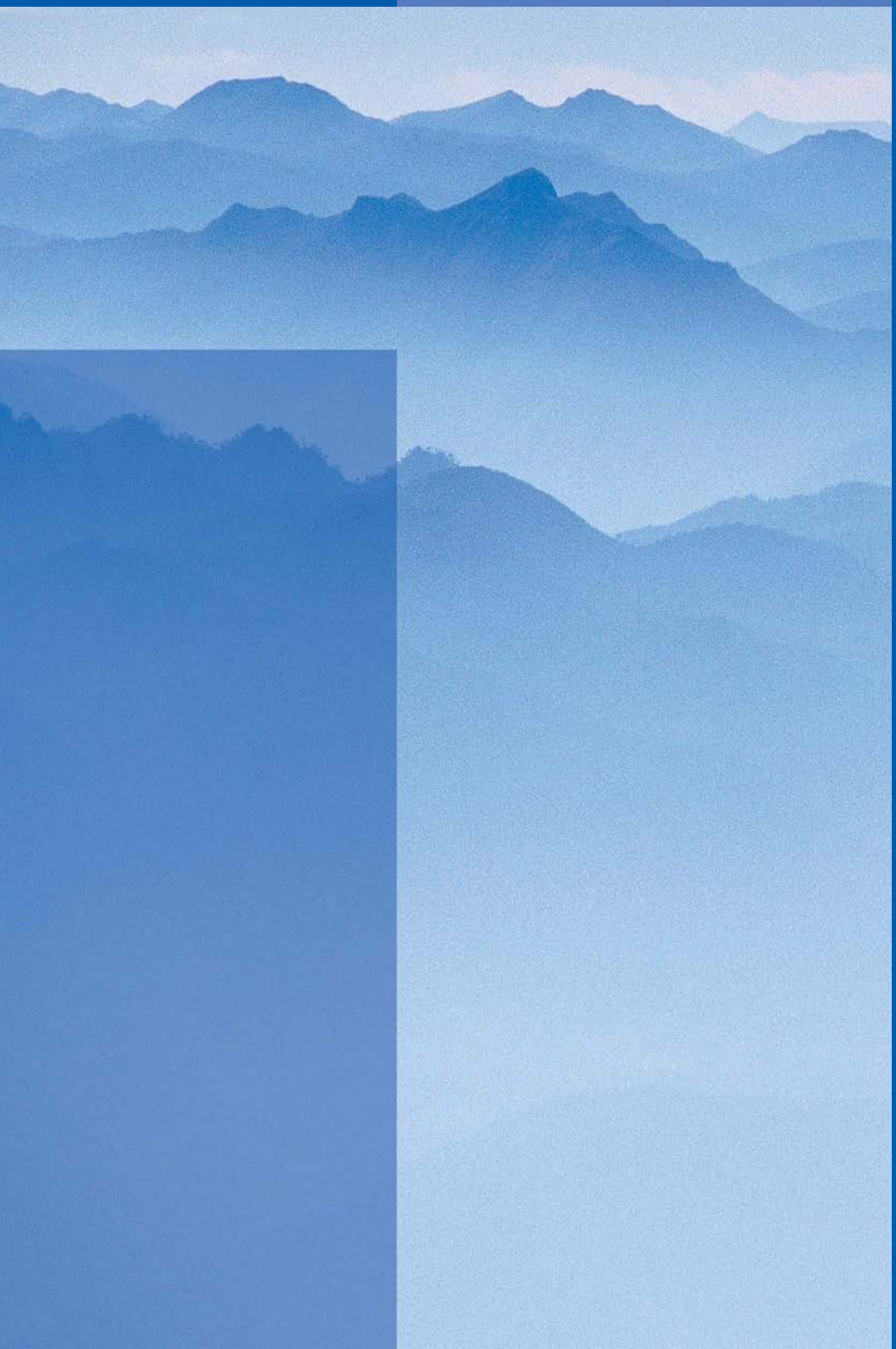
Phone _____

Fax _____

E-Mail _____

Please return to: Mental Health and Addictions, Ministry of Health Services, 1515 Blanshard Street, Victoria, BC V8W 3C8

Mheccu



Mental Health
Evaluation & Community
Consultation Unit

2250 Wesbrook Mall,

Vancouver, BC V6T 1W6

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Clinical Policy Bulletin:
Electroconvulsive Therapy
Number: 0445

Policy History
- Last Review: 10/11/2013
- Effective: 09/14/2000
- Next Review: 05/22/2014
- Review History
- Definitions

Additional Information
- Clinical Policy Bulletin Notes

Policy

1. Aetna considers electroconvulsive therapy (ECT) medically necessary for members diagnosed with any of the following conditions.

    1. Catatonia, *or*
    2. Certain acute schizophrenic exacerbations, *or*
    3. Major depression (unipolar, bipolar, or mixed episode), *or*
    4. Mania.

    Note: More than 20 sessions of ECT in a treatment series is rarely medically necessary.

2. Aetna considers multiple monitored ECT experimental and investigational because its effectiveness has not been established.

3. Aetna considers ultrabrief bilateral ECT experimental and investigational because its effectiveness has not been established.

4. Aetna considers ECT experimental and investigational for the treatment of the following interventions because its effectiveness for these indications has not been established (not an all inclusive list):

    - Body dysmorphic disorder
    - Complex regional pain syndrome (See CPB 0447 - Complex Regional Pain Syndrome (CRPS) / Reflex Sympathetic Dystrophy (RSD): Treatments)
    - Dementia-associated agitation and aggression
    - Obsessive-compulsive disorder
    - Post-traumatic stress disorder.

Background

Electroconvulsive therapy (ECT, also known as electroshock therapy) involves the intentional induction of generalized seizures by administering electrical impulses to the anesthetized patient. Treatments are typically administered by a psychiatrist and an

anesthesiologist or anesthetist.

Electroconvulsive therapy is generally administered in an inpatient setting, but can be administered on an outpatient basis in a facility with treatment and recovery rooms. It is usually administered 2 or 3 times a week, although ECT may be administered daily if tolerated.

The primary indication for ECT is major depressive disorder. Electroconvulsive therapy is usually considered when medications fail, can not be tolerated, or may be dangerous, but it is a first-line treatment for severely depressed patients who require a rapid response because of a high suicide or homicide risk, extreme agitation, life-threatening inanition, psychosis, or stupor. The average course of treatment for depression is 6 to 12 treatments, but some patients may require as many as 20 treatments.

Electroconvulsive therapy has been found to be as or more effective than lithium in the treatment of manic episodes and is also a potential treatment for patients experiencing mixed episodes. It is generally reserved for those patients with bipolar disorder who are unable to safely wait until a medication becomes effective, who are not responsive to or unable to safely tolerate one of the effective medications, is preferred by the patient in consultation with the psychiatrist, or who have had a good response to ECT in the past. The number of ECT treatments reported to be effective for mania has ranged from 8 to 20.

Electroconvulsive therapy is not effective for chronic schizophrenia. However, ECT may be effective for psychotic schizophrenic exacerbations when affective symptomatology is prominent, in catatonic schizophrenia, and when there is a history of a prior favorable response to ECT. Schizophrenia may require 17 or more ECT treatments.

A small number of ECT treatments often reverse catatonia, a nonspecific symptom that can occur in mood disorders, schizophrenia, cognitive disorders, and medical and neurological illnesses. Up to 12 treatments may be required in some patients.

There is very limited evidence that ECT is effective for delirium. In addition, there may be considerable risks with ECT in medically unstable patients. For these reasons, the American Psychiatric Association (APA) (1999) concluded that ECT “has not been shown to be an effective treatment for general cases of delirium.” The APA recommends that ECT be “considered only rarely for patients with delirium due to specific etiologies such as neuroleptic malignant syndrome and should not be considered initially as a substitute for more conservative and conventional treatments.”

A few clinicians have reported the successful use of ECT in severe obsessive-compulsive disorder (OCD), anorexia nervosa, atypical psychosis, cycloid psychosis, epilepsy with alternating psychosis, and chronic pain disorder, but those disorders are not usually considered indications for ECT. Electroconvulsive therapy is not an effective treatment for body dysmorphic disoder, dysthymic disorder, neuroses, dissociative disorders, hypochondriasis, conversion disorder, substance-related disorders, and personality disorders. Dell'Osso and colleagues (2005) noted that in addition to pharmacological, behavioral, and neurosurgical interventions, different brain stimulation methods such as transcranial magnetic stimulation, deep brain stimulation, as well as ECT have been examined in treatment-resistant patients with OCD. However, available data about the use of these techniques in OCD treatment are quite limited in terms of sample size and study design, given the difficulty in conducting standard blinded trials for these procedures. Furthermore, none of the mentioned treatments has received approval for the treatment of OCD from the Food and Drug Administration. This is in agreement with the observation of Schruers et al (2005) who stated that serotonin reuptake inhibitors

augmentation strategies with a variety of drugs and ECT have demonstrated results in individual cases, but no conclusive evidence has been found in placebo-controlled trials. In addition, the National Institute for Health and Clinical Excellence (NICE, 2006) guidelines on OCD stated that there is insufficient evidence on which to base a recommendation for the use of ECT in the treatment of OCD, especially given potential associated risks with ECT. Furthermore, the NICE report stated that there is no evidence that ECT or psychosurgery is beneficial in treating patients with body dysmorphic disorder.

Clinical experience suggests that ECT be continued until the patient has shown a maximal response; there is no evidence that administering 1 or 2 additional treatments results in a better outcome. Indeed, increased confusion from additional treatments may produce clinical deterioration. Electroconvulsive therapy is discontinued in patients who have had a partial but substantial improvement but show no change after 2 more treatments and in patients who have not responded at all after 6 to 10 treatments.

Prophylactic ECT may be needed for patients who do not tolerate or respond to prophylactic medications or who respond better to ECT. After remission, prophylactic ECT treatments are initially administered at weekly intervals, and the frequency of treatments is usually decreased gradually to once a month or less. Treatment has been continued for periods of 4 or 6 months to five years or longer; some patients apparently require indefinite prophylactic ECT.

Relative contraindications to ECT include space-occupying lesions of the brain, high intracranial pressure, intracerebral bleeding, recent myocardial infarction, retinal detachment, pheochromocytoma, high anesthesia risk, adolescents and children, or a significant medical illness in which risk outweighs potential benefit.

In multiple monitored electroconvulsive therapy (MMECT), a patient undergoes ECT in the usual manner, but before regaining consciousness, undergoes another session of ECT designed to elicit a second (or additional) seizure. The effectiveness of MMECT has not been established. The National Institutes of Health 1985 Consensus Development Conference Statement on ECT states that “Multiple monitored ECT (several seizures during a single treatment session) has not been demonstrated to be sufficiently effective to be recommended…”.

In an open, prospective study, Margoob et al (2010) examined the effects of ECT in the treatment of patients with chronic, severe, antidepressant- and congitive behavioral therapy (CBT)-refractory post-traumatic stress disorder (PTSD). A total of 20 consenting adults were prospectively treated with a fixed course of 6 bilateral ECT treatments administered on an outpatient basis at a twice-weekly frequency. The primary outcome measure was improvement on the Clinician-Administered Post-traumatic Stress Disorder Scale (CAPS). Baseline refractoriness was defined as a failure to respond to an adequate course of at least 4 different antidepressant drugs along with 12 sessions of CBT. Response to ECT was defined as at least 30 % attenuation of CAPS ratings, and remission as an end point CAPS score of 20 or less. After ECT, patients were prescribed sertraline (100 to 150 mg/day) or mirtazapine (15 to 30 mg/day). All but 3 patients completed the ECT course. An intent-to-treat analysis (n = 20) showed statistically and clinically significant improvement in the sample as a whole: CAPS scores decreased by a mean of 34.4 %, and depression scores by a mean of 51.1 %. Most of the improvement in CAPS and depression ratings developed by the third ECT; that is, by day 10 of treatment, itself. The improvement in CAPS ratings was independent of the improvement in depression ratings; and improvement in CAPS did not differ significantly between patients with less severe versus more severe baseline depression. The response rate was

70 %; no patient remitted. In the completer analysis (n = 17), mean improvements were 40 % and 57 % for CAPS and depression ratings, respectively, and the response rate was 82 %. Treatment gains were maintained at a 4 to 6 month follow-up. The authors concluded that ECT may improve the core symptoms of PTSD independently of improvement in depression, and may therefore be a useful treatment option for patients with severe, chronic, medication- and CBT-refractory PTSD. The findings of this small study need to be validated by well-designed studies.

Ujkaj et al (2012) examined the safety and effectiveness of ECT for agitation and aggression in dementia patients. A total of 16 patients with a diagnosis of dementia treated with ECT for agitation/aggression during 2004 to 2007 were included in this analysis. Clinical charts were rated on the Pittsburgh Agitation Scale as the primary outcome; the Clinical Global Impression scale and the Global Assessment of Functioning pre- and post-ECT were also used. Patients of mean age 66.6 +/- 8.3 years were studied. Their average overall and pre-ECT lengths of stay were 59.7 +/- 39.7 days and 23 +/- 15.7 days, respectively. Patients received a mean of 9 ECT treatments, mostly bilateral. Patients showed significant reductions in their total Pittsburgh Agitation Scale scores from baseline after ECT (from 11.0 +/- 5.0 to 3.9 +/- 4.3 [$F = 30.33$, $df = 1, 15$, $p < 0.001$]). Clinical Global Impression scale decreased significantly (from 6.0 +/- 0.6 pre-ECT to 2.1 +/- 1.6 post-ECT [$F = 112.97$, $df = 1, 15$, $p < 0.001$]). Global Assessment of Functioning change was not significant (from 23.0 +/- 4.9 to 26.9 +/- 6.9 [$F = 5.73$, $df = 1, 13$, $p = 0.32$]). Only 1 patient, in whom ECT was discontinued following 11 bilateral treatments, showed no improvement; 8 patients showed transient postictal confusion, which typically resolved within 48 hours. Two patients showed more severe postictal confusion that required modification of treatment. The authors concluded that these results suggested that ECT is an effective and safe treatment for agitation and aggression in dementia. Moreover, they stated that further prospective studies are warranted.

Oudman (2012) noted that depression is one of the most frequently diagnosed psychiatric disorders in patients with dementia with a prevalence of up to 50 %. The detrimental effects of depression in dementia include disability in daily living, worse quality of life, and faster cognitive decline. Although ECT is a well-established and effective treatment for depression in the elderly, it is currently an over-looked treatment option in the elderly with dementia and depression. The aim of this review was to provide a critical analysis of the safety and effectiveness of ECT in depression super-imposed on dementia by reviewing the current literature on this topic. Current evidence suggests that ECT is an effective treatment for depression in dementia, although the relatively small number of controlled studies hampers the comparison of effectiveness between healthy non-geriatric patients and those with dementia. Moreover, the systematic reports on cognitive side effects are very limited in number and currently only apply to moderately mild or mild dementia of non-vascular origin. Some studies do suggest that cognitive side effects are likely in later stages of dementia and in patients with vascular dementia. The author concluded that it is therefore of crucial relevance to prospectively study effects of ECT in different types and phases of dementia in controlled trials.

Loo and colleagues (2012) noted that the effect of shortening the pulse width of the electrical stimulus when administering ECT has recently been systematically studied with promising results. These investigators examined outcomes from 3 randomized controlled trials that compared ultrabrief (less than or equal to 0.3 ms) with brief (0.5 to 1.5 ms) pulse width ECT, and other recent clinical trials of ultrabrief pulse width ECT. The emerging evidence for ultrabrief pulse right unilateral (RUL) ECT suggested clinically meaningful efficacy and substantially reduced neuropsychological side effects compared with standard (brief) pulse ECT; this may represent a generational advance in the ECT technique. However, it is unclear if patients receiving ultrabrief pulse RUL ECT may

have a slower speed of response and require additional treatments compared with brief pulse ECT. Therefore, until further data are available, clinicians may be well advised to use brief pulse ECT in situations requiring an urgent clinical response. The authors concluded that the evidence base for ultrabrief bilateral ECT is limited, with findings that efficacy may be reduced compared with brief pulse width ECT. They stated that ultrabrief bilateral ECT should not be used outside the research setting.

Appendix

Selection Criteria for ECT:

1. Member has one of the qualifying psychiatric conditions listed in the policy section above; *and*
2. Member is at least 12 years of age; *and*
3. One of the following criteria is met:

    1. Member is unresponsive to effective medications, given for adequate dose and duration, that are indicated for the member's condition (e.g., anti-depressants, anti-psychotics, etc., as appropriate); *or*
    2. Member is unable to tolerate effective medications or has a medical condition for which medication is contraindicated; *or*
    3. Member has had favorable responses to ECT in the past, *or*
    4. Member is unable to safely wait until medication is effective (e.g., due to life-threatening inanition, psychosis, stupor, extreme agitation, high suicide or homicide risk, etc.); *or*
    5. Member is experiencing severe mania or depression during pregnancy; *or*
    6. Member prefers ECT as a treatment option in consultation with the psychiatrist.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

00104

90870

ICD-9 codes covered if selection criteria are met:

291.0 - 294.9	Organic psychotic conditions
295.00 - 299.91	Other psychoses
311	Depressive disorder, not elsewhere classified

ICD-9 codes not covered for indications listed in the CPB:

290.0 - 290.9	Dementias
300.00 - 300.9	Anxiety, dissociative and somatoform disorders
301.0 - 301.9	Personality disorders
303.00 - 305.93	Alcohol dependence syndrome, drug dependence, and nondependent abuse of drugs
309.81	Post-traumatic stress disorder
337.20 - 337.29	Reflex sympathetic dystrophy

The above policy is based on the following references:

1. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. Am J Psychiatry. 1994;151(12 Suppl):1-36.
2. American Psychiatric Association. Practice guideline for major depressive disorder in adults. Am J Psychiatry. 1993;150(4 Suppl):1-26.
3. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry. 1997;154(4 Suppl):1-63.
4. Dubovsky SL. Electroconvulsive therapy. In: Comprehensive Textbook of Psychiatry. 6th ed. HI Kaplan and BJ Sadock, eds. Baltimore, MD: Williams & Wilkins; 1995:2129-2140.
5. American Psychiatric Association. Practice guideline for the treatment of patients with delirium. Am J Psychiatry. 1999;156(5 Suppl):1-20.
6. McClellan J, Werry J; American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 1997;36 (10 Suppl):157S-176S.
7. American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry. 1998;37(10 Suppl):63S-83S.
8. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. Electroconvulsive therapy. National Institutes of Health Consensus Development Conference Statement. Natl Inst Health Consens Dev Conf Consens Statement. 1985 June 10-12;5(11):1-23. Available at: http://consensus.nih.gov/cons/051/051_statement.htm. Accessed July 7, 2005.
9. U.S. Department of Health and Human Services, Office of the Inspector General. Medicare reimbursement for electroconvulsive therapy. OEI-12-01-00450. Washington, DC; U.S. Department of Health and Human Services; December 2001. Available at: http://oig.hhs.gov/oei/reports/oei-12-01-00450.pdf. Accessed July 7, 2005.
10. Abdulwadud O. Electro convulsive therapy (ECT) in the management of bipolar mood disorder during pregnancy. Evidence Centre Critical Appraisal. Clayton, VIC: Centre for Clinical Effectiveness (CCE); 2001.
11. Bauer M, Whybrow PC, Angst J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depressions. World J Biol Psychiatry. 2002;3(2):69-86.
12. Grunze H, Kasper S, Goodwin G, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders. Part I: Treatment of bipolar depression. World J Biol Psychiatry. 2002;3(3):115-124.
13. Banken R. The use of electroconvulsive therapy in Quebec. AETMIS 02-05 RE. Montreal, QC: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS); 2002.
14. Grunze H, Kasper S, Goodwin G, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders, Part II: Treatment of Mania. World J Biol Psychiatry. 2003;4(1):5-13.
15. National Institute for Clinical Excellence (NICE). Guidance on the use of electroconvulsive therapy. Technology Appraisal 59. London, UK: NICE; April 2003. Available at: http://www.nice.org.uk/Docref.asp?d=68306. Accessed February 4, 2004.
16. Geddes J, Carney S, Cowen P, et al. Efficacy and safety of electroconvulsive

therapy in depressive disorders: A systematic review and meta-analysis. Lancet. 2003;361(9360):799-808.
17. Kho KH, van Vreeswijk MF, Simpson S, Zwinderman AH. A meta-analysis of electroconvulsive therapy efficacy in depression. J ECT. 2003;19(3):139-147.
18. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161(2 Suppl):1-56.
19. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Multiple Electroconvulsive Therapy (MECT) (160.25). Medicare Coverage Database. Baltimore, MD: CMS; April 1, 2004.
20. Ellis P; Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression. Australian and New Zealand clinical practice guidelines for the treatment of depression. Aust N Z J Psychiatry. 2004;38(6):389-407.
21. Ghaziuddin N, Kutcher SP, Knapp P, et al. Practice parameter for use of electroconvulsive therapy with adolescents. J Am Acad Child Adolesc Psychiatry. 2004;43(12):1521-1539.
22. Van der Wurff FB, Stek ML, Hoogendijk WL, Beekman ATF. Electroconvulsive therapy for the depressed elderly. Cochrane Database Syst Rev. 2003; (2):CD003593.
23. Greenhalgh J, Knight C, Hind D, et al. Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: Systematic reviews and economic modelling studies. Health Technol Assess. 2005;9(9):1-170.
24. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. Cochrane Database Syst Rev. 2005;(2):CD000076.
25. American Psychiatric Association. The practice of electroconvulsive therapy: Recommendations for treatment, training, and privileging: A task force report of the American Psychiatric Association, 2nd ed. Washington, DC: American Psychiatric Association Press; 2001.
26. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. Am J Psychiatry. 2002;159(4 Suppl):1-50.
27. Ciapparelli A, Dell'Osso L, Tundo A, et al. Electroconvulsive therapy in medication-nonresponsive patients with mixed mania and bipolar depression. J Clin Psychiatry. 2001;62(7):552-555.
28. Devanand DP, Polanco P, Cruz R, et al. The efficacy of ECT in mixed affective states. J ECT. 2000;16(1):32-37.
29. Gruber NP, Dilsaver SC, Shoaib AM, et al. ECT in mixed affective states: A case series. J ECT. 2000;16(2):183-188.
30. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry. 2000;157(4 Suppl):1-45.
31. Schruers K, Koning K, Luermans J, et al. Obsessive-compulsive disorder: A critical review of therapeutic perspectives. Acta Psychiatr Scand. 2005;111(4):261-271.
32. Dell'Osso B, Altamura AC, Allen A, Hollander E. Brain stimulation techniques in the treatment of obsessive-compulsive disorder: Current and future directions. CNS Spectr. 2005;10(12):966-979, 983.
33. Cybulska EM. Obsessive-compulsive disorder, the brain and electroconvulsive therapy. Br J Hosp Med (Lond). 2006;67(2):77-81.
34. National Institute for Health and Clinical Excellence (NICE). Obsessive compulsive disorder: Core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder. Clinical Practice Guideline No. 31. London, UK; NICE; January 25, 2006. Available at: http://www.nice.org.uk/page.aspx?o=289817. Accessed May 23, 2007.
35. McLoughlin DM, Mogg A, Eranti S, et al. The clinical effectiveness and cost of

repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: A multicentre pragmatic randomised controlled trial and economic analysis. Health Technol Assess. 2007;11(24):1-54.
36. Valentí M, Benabarre A, García-Amador M, et al. Electroconvulsive therapy in the treatment of mixed states in bipolar disorder. Eur Psychiatry. 2008;23(1):53-56.
37. Wilkins KM, Ostroff R, Tampi RR. Efficacy of electroconvulsive therapy in the treatment of nondepressed psychiatric illness in elderly patients: A review of the literature. J Geriatr Psychiatry Neurol. 2008;21(1):3-11.
38. Soomro GM. Obsessive compulsive disorder (updated). In: BMJ Clinical Evidence. London, UK: BMJ Publishing Group; August 2007.
39. Barbui C, Butler R, Ciprani A, et al. Depression in adults: Drug and physical treatments. In: BMJ Clinical Evidence. London, UK: BMJ Publishing Group; April 2006.
40. Hazell P. Depression in children and adolescents (updated). In: BMJ Clinical Evidence. London, UK: BMJ Publishing Group; April 2008.
41. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. Cochrane Database Syst Rev. 2008;(4):CD003437.
42. Rasmussen KG, Mueller M, Rummans TA, et al. Is baseline medication resistance associated with potential for relapse after successful remission of a depressive episode with ECT? Data from the Consortium for Research on Electroconvulsive Therapy (CORE). J Clin Psychiatry. 2009;70(2):232-237.
43. van Herck E, Sienaert P, Hagon A. Electroconvulsive therapy for patients with intracranial aneurysms: A case study and literature review. Tijdschr Psychiatr. 2009;51(1):43-51.
44. Kennedy SH, Milev R, Giacobbe P, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J Affect Disord. 2009;117 Suppl 1:S44-S53.
45. Lévy-Rueff M, Gourevitch R, Lôo H, et al. Maintenance electroconvulsive therapy: An alternative treatment for refractory schizophrenia and schizoaffective disorders. Psychiatry Res. 2010;175(3):280-283.
46. Consoli A, Benmiloud M, Wachtel L, et al. Electroconvulsive therapy in adolescents with the catatonia syndrome: Efficacy and ethics. J ECT. 2010;26(4):259-265.
47. Margoob MA, Ali Z, Andrade C. Efficacy of ECT in chronic, severe, antidepressant- and CBT-refractory PTSD: An open, prospective study. Brain Stimul. 2010;3(1):28-35.
48. Ujkaj M, Davidoff DA, Seiner SJ, et al. Safety and efficacy of electroconvulsive therapy for the treatment of agitation and aggression in patients with dementia. Am J Geriatr Psychiatry. 2012;20(1):61-72.
49. Oudman E. Is electroconvulsive therapy (ECT) effective and safe for treatment of depression in dementia? A short review. J ECT. 2012;28(1):34-38.
50. Dierckx B, Heijnen WT, van den Broek WW, Birkenhäger TK. Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: A meta-analysis. Bipolar Disord. 2012;14(2):146-150.
51. Loo CK, Katalinic N, Martin D, Schweitzer I. A review of ultrabrief pulse width electroconvulsive therapy. Ther Adv Chronic Dis. 2012;3(2):69-85.
52. Amanullah S, Delva N, McRae H, et al. Electroconvulsive therapy in patients with skull defects or metallic implants: A review of the literature and case report. Prim Care Companion CNS Disord. 2012;14(2).

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EVALUATION OF EVIDENCE: APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDERS

What are we trying to do? Oregon Senate Bill 365 was passed in 2013. This bill directs the Health Evidence Review Commission (HERC) to evaluate the evidence related to applied behavior analysis (ABA) for the treatment of autism spectrum disorder (ASD) in children that receive services as determined by the Prioritized List of Health Services under the Oregon Health Plan (OHP).

The history of coverage of treatment for ASD by OHP

1) This issue was last examined in 2008 by the Oregon Health Resources Commission. Currently, applied behavior analysis is not covered by OHP. Individuals may receive up to eight hours of treatment per month for the behaviors associated with ASD.
2) ASD often exists with other conditions, and these conditions have their own considerations for treatment, most of which are covered. Short-term rehabilitation and certain medicines are also covered.

What has been done so far?

1) HERC met August 8, 2013, discussed the process for completion of this evaluation of evidence, and referred the issue to the Evidence-based Guidelines Subcommittee (EbGS) for further discussion. On September 12, 2013, the EbGS reviewed the initial draft evaluation of evidence, heard public testimony and requested additional research by staff.
2) EbGS continued discussions at the November 7, 2013 meeting where it approved a draft evaluation of the evidence and preliminary conclusions that were released for public comment.
3) During a 30-day written public comment period that ended on December 16, 2013, 28 individuals submitted comments along with 356 citations for consideration.
4) Three ad hoc experts have been appointed to assist the subcommittee with its review of the evidence.
    a. Eric Fombonne, MD (Professor, OHSU Dept. of Psychiatry)
    b. Eric Larsson, PhD, LP, BCBA-D (Lovaas Institute for Early Intervention, Midwest Headquarters)
    c. Katharine Elizabeth Zuckerman, MD, MPH, FAAP (Assistant Professor, OHSU Division of General Pediatrics and Child and Adolescent Health Measurement Initiative)

5) The EbGS had planned to review public comments and continue discussions at its February 7 meeting, but the meeting was cancelled due to a snowstorm. A replacement meeting was held March 20, 2014. The subcommittee reviewed public comment, continued its discussion and provided staff with general direction for drafting recommendations.
6) On April 24, 2014 the EbGS met once again and finalized its recommendations.
7) On May 8, the Value-based Benefits Subcommittee discussed potential changes to coverage under the Oregon Health Plan.

What are the draft recommendations?

1) During its review to date, EbGS has determined that moderate-quality evidence indicates benefit for ABA in children with ASD between the ages of 1-12. The subcommittee also adopted criteria for continued coverage based on documented progress towards treatment goals and established intensity and duration limits.
2) EbGS also decided to offer more limited coverage for focused ABA in individuals with autism who are over the age of 12. This coverage would be limited to dealing with specific problematic behaviors.

What happens now?

1) The EbGS evaluation and conclusions will go to the Value-based benefits Subcommittee (VbBS) on June 12, 2014. VbBS will use the EbGS conclusions to determine what changes may be needed to the Prioritized List of Health Services and if there are any issues that would be involved in implementing these changes in OHP.
2) The evidence evaluation and any changes to the Prioritized List will eventually need final approval by the full HERC, which has members from many areas of health care (doctors, nurses, chiropractic, patients, health plan administrators, and more).
3) Any changes to the Prioritized List affecting OHP coverage of ABA would go into effect sometime between October 1, 2014 and April 1, 2015.

How can you participate?

1) You can subscribe to the HERC website at www.oregon.gov/OHA/OHPR/Pages/HERC/ to receive notifications of future meetings and look at materials being discussed.
2) You can attend the meetings, which are open to the public, and provide verbal testimony during time set aside for public comment.

Applied Behavioral Analysis for Autism Spectrum Disorders

Question: How should applied behavioral analysis (ABA) for autism spectrum disorder (ASD) be incorporated into the Prioritized List? Should the autism spectrum disorder line be rescored?

Question source: EbGS, HERC staff

Issue: See also ABA Overview and Update for details.

Senate Bill 365 (see attached for complete bill)
Oregon Senate Bill 365 was passed by the Oregon legislature in the 2013 regular session. That bill establishes requirements for state-regulated commercial health plans to approve and manage autism treatment, including ABA therapy and any other medical or mental health services identified in an individualized treatment plan. The law applies to patients who seek care before age nine, with a minimum covererage of up to 25 hours of ABA per week, and continuing as long as medically necessary. Health plans that provide coverage to OEBB and PEBB are required to begin coverage in 2015, and all other health plans are required to begin coverage in 2016. The bill required HERC to evaluate the evidence for ABA and make a coverage decision for OHP.

Applied behavior analysis is defined in the bill as the following:

> The design, implementation and evaluation of environmental modifications, using behavioral stimuli and consequences, to produce significant improvement in human social behavior, including the use of direct observation, measurement and functional analysis of the relationship between environment and behavior and that is provided by:
>
> > (i) A licensed health care professional registered under section 3 of this 2013 Act;
> >
> > (ii) A behavior analyst or an assistant behavior analyst licensed under section 3 of this 2013 Act; or
> >
> > (iii) A behavior analysis interventionist registered under section 3 of this 2013 Act.
>
> "Applied behavior analysis" excludes psychological testing, neuropsychology, psychotherapy, cognitive therapy, sex therapy, psychoanalysis, hypnotherapy and long-term counseling as treatment modalities.

EbGS has reviewed the evidence and adopted summary conclusions based on the evidence and a modified GRADE methodology. Expert input was solicited and reviewed. Public comment was solicited and reviewed. In addition to specific comments, a total of 336 unduplicated citations were provided by public commenters. Each citation was evaluated to determine study design or article type and population characteristics (number and ages of included individuals), the abstract was retrieved and a link to the article provided when available.

Given that the focus of most of the public comment pertained to requesting that ABA be recommended for coverage in individuals over age 12, detailed review of citations was limited to those studies. A random sample of 10% of SSRD study types (60 total) were reviewed in additional detail. In addition, all systematic reviews and meta-analyses of SSRDs were reviewed in more detail.

EbGS deliberations
EbGS met April 24, 2014, having reviewed the evidence, public written comment, in-person public comment, expert input and approved a modified Evidence Review Document to send to VbBS.

Staff additions
On further review of the requirements of the Medicaid Expansion and habilitative and mental health parity requirements of the ACA, staff suggests modifying the language to be more descriptive of studies and less directive of specific hour limits.

Current Prioritized List information:
Line: 313
Condition: AUTISM SPECTRUM DISORDERS (See Guideline Notes 64,65,75)
Treatment: CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION
ICD-9: 299.00-299.91
CPT: 90785,90832-90840,90846-90849,90882,90887,96101,96118,98966-98969,99051,99060,99201-99215,99224-99226, 99366,99441-99444,99487-99496
HCPCS: G0176,G0177,G0406-G0408,G0425-G0427, H0023, H0032, H0034, H0038, H2010, H2011, H2014,H2027,H2032, S0270,S0272-S0274,S9484,T1016

Current guideline
GUIDELINE NOTE 75, AUTISM SPECTRUM DISORDERS
Line 334
There is limited evidence of the effectiveness of treatment (e.g., Applied Behavioral Analysis) for Autism Spectrum Disorders (ASD). However, effective treatments may be available for co-morbid conditions such as mood disorders. When treating co-morbid conditions, that condition, not an ASD diagnosis, should be the primary diagnosis for billing purposes. The treatment of co-morbid mental health conditions should be consistent with the treatment methods, frequency, and duration normally applied to those diagnoses. Treatment of neurologic dysfunctions that may be seen in individuals with an ASD diagnosis are prioritized according to the four dysfunction lines found on the Prioritized List (Lines 78, 318, 375 and 407). Treatment for associated behaviors, such as agitation, that do not meet the criteria for co-morbid mental health diagnoses should be limited in frequency to a maximum of 8 hours of behavioral health

service per month, subject to utilization management review by the mental health organization (MHO) or other relevant payer.

New CPT codes for ABA therapy

1) New category III CPT codes have been published by the AMA effective July 1, 2014
    a. 0359T-0363T (adaptive behavior assessments)
    b. 0364T-374T (adaptive behavior treatments)
    c. See attached document submitted by Dr. Larsson for information on definition of these codes

Of note, DMAP has a rule that excludes the use of temporary codes. This rule would need to be deleted. As a result, there is a good likelihood of additional temporary codes being brought to VBBS/HERC for review in the future.

EbGS approved GRADE table

Indication/Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Values and preferences	Recommendation
Children aged 1 to 12 years at initiation					
Early Intensive Behavioral Interventions	Benefit on cognitive and language skills	Moderate	High	Low variability	Recommendation for coverage (strong recommendation)
	Benefit on adaptive behavior, social skills and overall autism severity	Low	High	Low variability	
Parent training interventions	Increased joint attention and parent synchrony, and improved early language and communication skills	Moderate	Moderate	Low variability	Recommendation for coverage (strong recommendation)

Indication/Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Values and preferences	Recommendation
	Lessened overall severity of autism and improved early cognition	Low	Moderate	Low variability	
Play/interaction-based interventions (including joint attention interventions)	Improvements in joint attention and language skills	Moderate	Low	Low variability	Recommendation for coverage (strong recommendation)
	Short-term improvements in play, imitation, social skills	Low	Low	Low variability	
Adolescents and young adults					
ABA	Unknown	Insufficient	Moderate for focused, high for more comprehensive	Low variability	Recommend noncoverage of intensive ABA therapies *(weak recommendation)* Recommendation for coverage for specific problem behaviors with targeted interventions *(weak recommendation)*

EBGS APPROVED SUMMARY CONCLUSIONS

Children ages 1 to 12

Applied behavior analysis (ABA), including early intensive behavioral intervention (EIBI), is recommended for coverage[1] for treatment of autism spectrum disorder[2] (*strong recommendation*).

> Rationale: This strength of recommendation was based on sufficient (moderate quality) evidence and expert input, including testimony on parent/caregiver values and preferences.

Specifically, EIBI (for example, UCLA/Lovaas or ESDM), is recommended for coverage for up to 25 hours per week for a maximum of three years.

> Rationale: The 25-hour limit would be similar to other payers in Oregon that were mandated through SB 365 and earlier Warren report had demonstrated 25 hours per week was effective. There is no evidence that increased intensity beyond this level yields improves outcomes. The duration limit is based on the fact that EIBI studies have a duration of 2-3 years

Initial coverage of EIBI should be provided for up to six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using standardized, multimodal assessments, no more frequently than every six months *(strong recommendation).* Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).

> Rationale: Ensuring that patients are making meaningful progress is important to ensure quality outcomes and effective use of resources. The six month assessment was chosen based on expert input and subcommittee deliberation to allow for sufficient time for progress while not being burdensome to providers and plans.

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[1] These conclusions apply to the Oregon Health Plan as governed by the Prioritized List of Health Services and to no other health plan.

[2] Autism spectrum disorder should be diagnosed by a qualified health care professional according to DSM-5 criteria.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are recommended for coverage to address core symptoms of autism and/or specific problem areas *(strong recommendation)* for up to 8 hours per month. In extenuating circumstances (e.g severe aggressive behavior that is responding to interventions but requires increased intensity), an additional 8 hours per month is recommended for coverage. Initial coverage should be provided for six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives or emergence of new problem behaviors.

> Rationale: Not all autistic children require comprehensive therapy and less intensive interventions will be appropriate for many, or appropriate for those who have completed intensive intervention. Evidence supports these less intensive interventions in this age group. Eight hours was chosen based on a wide range of intensity in the literature, expert input, and previous HERC Prioritized List guideline precedent.

Parent/caregiver involvement and training is recommended to be a component of treatment *(strong recommendation).*

> Rationale: Evidence and expert input indicated that parental involvement in ABA is a key part of effective treatment. Parent delivered therapy is effective.

<u>Individuals ages 13 and older</u>

Intensive ABA is not recommended for coverage for treatment of autism spectrum disorder in persons ages 13 and older (*weak recommendation*).

> Rationale: There is insufficient evidence to support intensive ABA treatment at older ages.

For individuals age 13 and older, targeted behavioral interventions, including focused ABA*, are recommended for coverage for up to 8 hours per month, up to 6 months, only to address specific problem behaviors (*weak recommendation*). Behaviors eligible for coverage include those which place the member at risk for

harm or create significant daily issues related to care, education, or other important functions. The interventions should involve predefined behavioral objectives that would result in socially important and sustainable outcomes for the individual. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives with ongoing proof of medical appropriateness, or emergence of new problem behaviors.

> Rationale: According to the trusted evidence source, there is insufficient evidence to support ABA-based interventions in this age group. Public comment and some expert testimony involved submission of many single subject research design studies to support treatment in this age group, but the quality of this evidence did not meet predetermined criteria for inclusion. The subcommittee agreed that problem behaviors can be challenging to the individual, caregivers, and society and it is reasonable to consider targeted interventions for specific problem behaviors as long as there are clear objectives, progress toward meaningful predefined goals and ongoing proof of medical appropriateness. The net result was to recommend targeted interventions including ABA-based treatments for limited intensity to address problem behaviors. Six months was chosen based on expert testimony and subcommittee discussion that more frequent assessments would potentially be burdensome to providers and plans.

Parent/caregiver involvement and training is encouraged *(weak recommendation)*

Note: The evidence for the treatment of conditions comorbid with autism spectrum disorder is beyond the scope of this evidence summary.

HERC STAFF RECOMMENDATIONS:

1) Delete current guideline note 75
2) Add a replacement guideline note

GUIDELINE NOTE 75 APPLIED BEHAVIORAL ANALYSIS FOR AUTISM SPECTRUM DISORDER
Line 313

Applied behavioral analysis (ABA), including early intensive behavioral intervention (EIBI), represented by CPT codes 0359T-0374T, is included on line 313 for the treatment of autism spectrum disorders.

Individuals ages 1-12

Intensive interventions
Specifically, EIBI (for example, UCLA/Lovaas or Early Start Denver Model), is included on this line.

For a child initiating EIBI therapy, EIBI is included for up to six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using a standardized, multimodal assessment, no more frequently than every six months. Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).

The evidence does not lead to a direct determination of optimal intensity. Studies of EIBI ranged from 15-40 hours per week. Through Oregon's Senate Bill 365, other payers are mandated to cover a minimum of 25 hours per week of ABA. There is no evidence that increasing intensity of therapy yields improves outcomes. Studies for these interventions had a duration from less than one year up to 3 years.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are included on this line to address core symptoms of autism and/or specific problem areas. Initial coverage is provided for six months. Ongoing coverage is based on demonstrated

progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Effective interventions from the research literature had lower intensity than EIBI, usually a few hours per week to a maximum of 16 hours per week, divided into daily, twice-daily or weekly sessions, over a period of several months.

Parent/caregiver involvement

Parent/caregiver involvement and training is recommended as a component of treatment.

Individuals ages 13 and older

Intensive ABA is not included on this line.

Targeted ABA-based behavioral interventions to address problem behaviors, are included on this line. The quality of evidence is insufficient to support these interventions in this population. However, due to strong caregiver values and preferences and the potential for avoiding suffering and expense in dealing with unmanageable behaviors, targeted interventions may be reasonable. Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Very low quality evidence is available to illustrate needed intensity and duration of intervention. In the single-subject research design literature, frequency and duration of interventions were highly variable, with session duration ranging from 30 seconds to 3 hours, number of sessions ranging from a total of three to 8 times a day, and duration ranging from 1 to 20 weeks. These interventions were often conducted in inpatient or residential settings and studies often included patients with intellectual disabilities, some of which were not diagnosed with autism.

Parent/caregiver involvement and training is encouraged.

3) Add CPT 0359T-0374T (adaptive behavior assessments and treatments) to line 313 AUTISM SPECTRUM DISORDERS

   a. Discuss if any further clarification about assessments versus interventions and types of providers should be addressed in the Prioritized List guideline
   b. See Dr. Larsson's submitted alternatives
4) Consider adding clarifying language to the new Guideline Note about how speech/PT/OT services for other qualifying conditions are covered when ABA is also being covered
   a. ABA services are provided in addition to any rehabilitative services (e.g. physical therapy, occupational therapy, speech therapy) included in guideline note 6, REHABILITATIVE THERAPIES that are indicated for other acute qualifying conditions.
5) Determine whether staff should look into adding a guideline about self-injury and other problem behaviors in non-autistic children
6) Recommend that EbGS view and revise their summary conclusions as time and meetings allows
7) Change treatment description of line: ~~CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION~~ MEDICAL THERAPY/BEHAVIORAL MODIFICATION INCLUDING APPLIED BEHAVIORAL ANALYSIS
8) Review prioritization scoring of the autism spectrum line as shown below

Scoring proposal (scoring for line 313 in parentheses)
Category: 3 (3)
HL: 5 (5)
Suffering: 4 (4)
Population effects: 1 (1)
Vulnerable population: 0 (0)
Tertiary prevention: ()
Effectiveness: 3 (2)
Need for service: 0.7 (0.7)
Net cost: 1 (3)
Score: 1575 (1050)

Approximate new line placement: 217

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

EVALUATION OF EVIDENCE: APPLIED BEHAVIORAL ANALYSIS FOR AUTISM SPECTRUM DISORDERS

DRAFT as approved by EbGS 4/24/2014

BACKGROUND

Oregon Senate Bill 365 was passed by the Oregon legislature in the 2013 regular session. That bill directs the Health Evidence Review Commission to evaluate applied behavioral analysis (ABA) as a treatment for autism spectrum disorder (ASD) for the purposes of updating the prioritized list of health services. The bill also establishes requirements for state-regulated health plans to approve and manage autism treatment, including ABA therapy and any other medical or mental health services identified in an individualized treatment plan. The law applies to patients who seek care before age nine, covering up to 25 hours of ABA per week, and continuing as long as medically necessary. Health plans that provide coverage to OEBB and PEBB are required to begin coverage in 2015, and all other health plans are required to begin coverage in 2016. Applied behavior analysis is defined in the bill as the following:

The design, implementation and evaluation of environmental modifications, using behavioral stimuli and consequences, to produce significant improvement in human social behavior, including the use of direct observation, measurement and functional analysis of the relationship between environment and behavior and that is provided by:

(i) A licensed health care professional registered under section 3 of this 2013 Act;

(ii) A behavior analyst or an assistant behavior analyst licensed under section 3 of this 2013 Act; or

(iii) A behavior analysis interventionist registered under section 3 of this 2013 Act.

“Applied behavior analysis” excludes psychological testing, neuropsychology, psychotherapy, cognitive therapy, sex therapy, psychoanalysis, hypnotherapy and long-term counseling as treatment modalities.

For details of the public process used to develop this evaluation of evidence, see http://www.oregon.gov/oha/herc/Pages/blog-ABA.aspx

EVIDENCE SOURCES

Warren, Z., Veenstra-VanderWeele, J., Stone, W., Bruzek, J.L., Nahmias, A.S., Foss-Feig, J.H., et al. (2011). *Therapies for children with autism spectrum disorders. Comparative effectiveness review no. 26.* (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I). AHRQ Publication No. 11-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2011. Retrieved from http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=651

Update of Warren 2011 in draft form:

Therapies for children with autism spectrum disorder – Behavioral interventions update. Draft Comparative Effectiveness Review. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved January 27, 2014, from http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=1845

Lounds Taylor, J., Dove, D., Veenstra-VanderWeele, J., Sathe, N.A., McPheeters, M.L., Jerome, R.N., et al. (2012). *Interventions for adolescents and young adults with Autism Spectrum Disorders. Comparative Effectiveness Review No. 65.* (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 12-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1197&pageaction=displayproduct

Maglione, M., Motala, A., Shanman, R., Newberry, S., Schneider Chafen, J., & Shekelle, P. (2012). *AHRQ Comparative Effectiveness Review Surveillance Program: Therapies for Children with Autism Spectrum Disorders, 2nd Assessment.* Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1536

Oono, I.P., Honey, E.J., & McConachie, H. (2013). Parent-mediated early intervention for young children with autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews*, Issue 4. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009774.pub2/abstract

- *List of included studies in Oono 2013 provided in Appendix D*

Glossary Sources

Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program. (n.d.). Glossary of terms. Retrieved from http://effectivehealthcare.ahrq.gov/index.cfm/glossary-of-terms/

National Cancer Institute (NCI) at the National Institutes of Health (NIH). (n.d.). NCI dictionary of cancer terms. Retrieved from http://www.cancer.gov/dictionary

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

The following clinical background summary is extracted from the update to the Warren 2011 report (AHRQ draft, 2014).

> Autism spectrum disorder (ASD) is a neurodevelopmental disorder marked by impaired social communication and social interaction accompanied by atypical patterns of behavior and interest. ASD is differentiated from other developmental disorders by significant impairments in social interaction and communication, along with restrictive, repetitive, and stereotypical behaviors and activities. Social communication and social interaction features include deficits in social-emotional reciprocity (e.g., deficits in joint attention, atypical social approach and response, conversational challenges, reduced sharing of interest, emotions, and affect), deficits in nonverbal communication (e.g., atypical eye contact, reduced gesture use, limited use of facial expressions in social interactions, challenges understanding nonverbal communication), and deficits in forming and maintaining relationships (e.g., diminished peer interest, challenges joining in play, difficulties adjusting behavior to social context). ASD features of restricted, repetitive patterns of behavior, interests, or activities may include stereotyped motor mannerisms, use of objects, or speech (e.g., simple motor stereotypies, repetitive play, echolalia, and formal or idiosyncratic speech); insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior (e.g., distress at small changes, rigid patterns of thought and behavior, performance of everyday activities in ritualistic manner); intense preoccupation with specific interests (e.g., strong attachment to objects, circumscribed or perseverative topics of interest); and sensory sensitivities or interests (e.g., hyper- or hypo-reactivity to pain and sensory input, sensitivity to noise, visual fascination with objects or movement). These symptoms cause impairment across many areas of functioning and are present early in life. However, impairments may not be fully evident until environmental demands exceed children's capacity. They also may

be masked by learned compensatory strategies later in life. Many children with ASD may also have intellectual impairment or language impairment, and the disorder may be associated with known medical, genetic, or environmental factors. (p. ES-1)

The prevalence of ASD in the United States is 11.3 cases per 1,000 (or 1 in 88) children living in the communities surveyed, with rate estimates varying widely by region of the country, sex, and race/ethnicity. Considerably more males (1 in 54) than females (1 in 252) are affected. For some individuals, the core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and maturation; however, core deficits typically translate into varying developmental presentations that remain throughout the lifespan. Longitudinal studies indicate that adults with ASD struggle to obtain adaptive independence. (p. 1)

Treatments for ASD include behavioral, educational, medical, allied health, and complementary approaches. Individual goals for treatment vary for different children and may include combinations of therapies. For many individuals, core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and over time5-8; however, deficits typically remain throughout the lifespan. Chronic management—often using multiple treatment approaches—may be required to maximize ultimate functional independence and quality of life. (p. ES-1)

This review of the evidence addresses only behavioral interventions for ASDs that utilize principles of applied behavior analysis (ABA).

ABA is an umbrella term describing principles and techniques used in the assessment, treatment and prevention of challenging behaviors and the promotion of new desired behaviors. The goal of ABA is to teach new skills, promote generalization of these skills, and reduce challenging behaviors with systematic reinforcement. The principles and techniques of ABA existed for decades prior to specific application and study within ASDs. (AHRQ draft, 2014, p. 5)

Interventions that utilize the principles of ABA include comprehensive treatments referred to as Early Intensive Behavioral and Developmental Interventions (EIBI). Two of these intensive treatments have been manualized (i.e., have published treatment manuals to facilitate replication): the UCLA/Lovaas model and the Early Start Denver Model (ESDM). There are other treatment approaches that also incorporate ABA principles, and may be intensive in nature, but have not been manualized. A third particular set of interventions include those using the principles of ABA to focus on key

pivotal behaviors rather than global improvements. These approaches emphasize parent training as a modality for treatment delivery (e.g., Pivotal Response Training, Hanen More than Words, social pragmatic intervention, etc.) and may focus on specific behaviors such as initiating or organizing activity or on core social communication skills.

Play-/interaction-based interventions may employ ABA principles and are included in this review. These interventions use interactions between children and adults (either parents or researchers) to improve outcomes such as imitation or joint attention skills or the ability of the child to engage in symbolic play. They include teaching parents how to interact differently with their children within daily routines and interactions, often using standard behavior management strategies.

Evidence Review

Children Ages Two to Twelve

EIBI and Other ABA Interventions

Warren (2011)

The Warren (2011) AHRQ review included all study designs as long as there were at least 10 participants. A total of 30 discrete studies were included, with the largest study population being 78 participants. The longest duration of treatment in any included study was three years. The mean age of children at intake in the included studies ranged from 21 to 66 months for EIBI interventions and from 42 months to 10.8 years for other ABA interventions. Authors reach the following conclusions:

> The evidence suggests that early intensive behavioral and developmental intervention (EIBI) may improve core areas of deficit for individuals with ASDs; however, randomized controlled trials (RCTs) are few and include small numbers of participants. In addition, there are no direct comparison trials. "Within this category, studies of UCLA/Lovaas-based interventions report greater improvements in cognitive performance, language skills, and adaptive behavior skills than broadly defined eclectic treatments available in the community. However, strength of evidence is currently low" (Warren, 2011, p. ES-7). In addition, the consistency of benefit is lacking, in that "not all children demonstrate rapid gains, and many children continue to display substantial impairment" (Warren, 2011, p. ES-7). Although positive results are reported for the effects of intensive interventions that use a developmental framework, such as ESDM, evidence for this type of intervention is currently insufficient because few studies have been published to date.

Less intensive interventions focusing on providing parent training for bolstering social communication skills and managing challenging behaviors have also been studied. Some interventions have shown short-term gains in social communication and language use, but the current evidence base for such treatment remains insufficient. Strength of evidence is also considered insufficient for play- and interaction-based approaches.

Only one study was identified that directly addressed whether there are any modifiers of outcomes for different ABA-based behavioral approaches. It examined the impact of which provider (parent vs. professional) delivered the UCLA/Lovaas protocol-based interventions. There was no significant difference in outcomes for children receiving the intervention in a clinical setting vs. at home from highly trained parents.

Other potential correlates that warrant further study because of conflicting data include pretreatment IQ and language skills, and age of initiation of treatment (with earlier age potentially associated with better outcomes). “Social responsiveness and imitation skills have been suggested as skills that may correlate with improved treatment response in UCLA/Lovaas treatment, whereas ‘aloof’ subtypes of ASDs may be associated with less robust changes in IQ. Other studies have seen specific improvement in children with PDD-NOS vs. Autistic Disorder diagnoses, which may be indicative of baseline symptom differences. However, many other studies have failed to find a relationship between autism symptoms and treatment response” (Warren, 2011, p. ES-8).

“Research on very young children is preliminary, with four studies identified. One good-quality RCT suggested benefit from the use of ESDM in young children, with improvements in adaptive behavior, language, and cognitive outcomes. Diagnostic shifts within the autism spectrum were reported in close to 30 percent of children but were not associated with clinically significant improvements in Autism Diagnostic Observation Schedule severity scores or other measures” (Warren, 2011, p. ES-9).

There was no evidence identified in the Warren review that addressed treatment effectiveness in specific subgroups such as race, ethnicity, gender or socioeconomic status, other than age. Details of all comparative studies that reported comparative statistics are provided in the table below.

Table 1. Comparative Studies included in Warren 2011

Author	Study Design	Intervention Intensity	Intervention Duration	Summary of Outcome
Smith 2000	RCT, intensive vs. parent training	Intensive: 30 hrs/wk with therapist, 5	intensive: 2-3 yrs	Intensive group had improved IQ, developmental

Author	Study Design	Intervention Intensity	Intervention Duration	Summary of Outcome
		hrs/wk with parents X 3 months Parent: taught techniques from Lovaas manual 2 sessions/wk	parent: 3-9 mos	scores compared to parent training, as well as in 1 communication score, but not in 3 others, and no sig diff in adaptive function MIXED
Drew 2002	RCT, parent training vs. local services (ST, OT, ABA, home worker)	Parent: 6.3 hrs/wk Local: 3.5 hrs/wk	Not specified; follow up at 1 year	No sig diff between groups in cognitive[1] outcomes. parent group had some better communication outcomes MIXED
Aldred 2004	RCT, social communication intervention vs. routine care (not described)	Intervention: monthly treatment sessions X 6 months (time not specified), then less frequent for another 6 months Control: routine care	1 year	Intervention group had better language scores, parent synchrony. No diff in shared attention MIXED
Eikeseth 2002/ 2007	Non-randomized CT, Lovaas behavioral treatment vs. eclectic (TEACCH, sensory-motor therapies, ABA)	Lovaas: 28 hrs/wk Eclectic: 29 hrs/wk	Not specified; first follow up at 1 year	Lovaas group had sig more improvement than eclectic in IQ, communication, adaptive behavior at both 1 and 8 year follow up for most measures POSITIVE
Reed 2007	Non-randomized CT, high intensity ABA vs. low intensity ABA	High: mean 30 hrs/wk Low: mean 13 hrs/wk	Not specified	No diff in autism severity, adaptive behavior. Mixed result for cognitive, with high intensity scoring better on one measure but not another MIXED
Howard 2005	Prospective cohort, intensive ABA vs. intensive eclectic (delivered in school) vs. non-intensive public early intervention	ABA: 25-30 hrs/wk for age <3, 35-40 for age >3 plus parent training Intensive eclectic: not specified Public EI: not specified	Follow up at 14 mos	ABA group had sig higher scores than mean of the other two groups for all outcome measures except motor skills POSITIVE
Remington	Prospective cohort,	EI: mean 26 hrs/wk	2 years	EI group had sig higher

[1] Educational, cognitive, and academic outcomes are reported together and noted as "cognitive" unless specified otherwise.

Author	Study Design	Intervention Intensity	Intervention Duration	Summary of Outcome
2007	home-based early intervention (parent delivered with tutors) vs. local education standard treatment	Control: not specified		scores for most outcomes, including social skills, communication, adaptive behavior, cognitive function POSITIVE
Cohen 2006	Prospective cohort, EIBI (Lovaas) vs. services from public school (parent choice)	Intervention: 35-40 hrs/wk, 47 wks/yr Control: not specified	3 years	Intervention group had higher IQ, were more likely in regular classroom and had higher adaptive scores; no sig diff in communication POSITIVE
Stahmer 2001	Prospective cohort, parent information support group and education course on PRT vs. education course only (control)	2 hrs/week for intervention group vs 1 hr/wk for control	12 weeks	Sig more parents in the intervention group correctly used PRT techniques, and their children had improved communication POSITIVE
Zachor 2007 (appears to be a subset of Itzchak 2009)	Prospective cohort, behavioral vs. eclectic	Behavioral: 1 to 1 35 hrs/wk Eclectic: special ed teacher, various therapists (OT, ST), parent training, at least 16 hrs/wk	Not specified	Sig improved overall severity, communication behavioral group compared to eclectic, no sig diff in social skills POSITIVE
Hayward 2009/ Eikeseth 2009	Prospective cohort, clinic based vs. parent managed	Clinic: 37 hrs/week Parent: 34 hrs/week (mean supervision hrs/mo = 5)	1 year	No differences between groups in communication, adaptive behavior, cognitive/academic NEGATIVE
Eldevik 2006	Retrospective cohort, low intensity behavioral (Lovaas) vs. eclectic (alternative communication, TEACCH, sensory-motor, ABA	Behavioral: 12 hrs/wk Eclectic: not specified	Behavioral: 20 mos Eclectic: 21 mos	Behavior group had mixed outcomes on cognitive measures (better on some measures, no diff on others), better communication scores, fewer problem behaviors. no diff in adaptive scores MIXED
Reed 2007	Retrospective cohort, ABA vs. special nursery vs. portage (parent training)	ABA: mean 30 hrs/wk Special nursery: mean 12 hrs/wk Portage: mean 8 hrs/wk	Not specified	27 diff outcomes measures reported on, no sig diffs on 18. ABA group had better scores than one or the other of the comparators for the following measures: 2 of 3 overall ratings, 4 of 8 communication scores, 3 of

Author	Study Design	Intervention Intensity	Intervention Duration	Summary of Outcome
				7 behavior scores. There were no diffs in motor skills scores, cognitive scores, comorbidities MIXED

In summary, the intensity of experimental interventions ranged from less than two hours per week to 40 hours per week. For the control interventions, intensity was often not specified, but was as high as 34 hours per week. Of those studies showing a mostly positive outcome for the intervention, intensity ranged from 26 to 40 hours per week, with the exception of the Stahmer study, which was a very narrowly focused intervention aimed at teaching parents a specific skill.

With regard to duration, five studies did not specify the length of the intervention period. The shortest study was 12 weeks, while the longest was 3 years. Of those studies showing a mostly positive outcome for the intervention, duration ranged from no more than a year to three years, with the exception of the Stahmer study.

The following limitations of the evidence were noted by the report authors:

> A high proportion of studies in this review (36 percent) fail to use a comparison group, and while substantial strides have been made in the analysis of single-subject designs, these are not ideal for assessing effectiveness at a population level, nor are they appropriate for comparative effectiveness research. They are, however, used frequently in the behavioral literature, and so we address our decisions regarding them here. Because there is no separate comparison group in these studies they would be considered case reports (if only one child included) or case series (multiple children) under the rubric of the EPC study designs. Case reports and case series can have rigorous evaluation of pre- and post-measures, as well as strong characterization of the study participants.
>
> Studies using this design that included at least 10 children were included in the review. Studies of this type can be helpful in assessing response to treatment in very short time frames and under very tightly controlled circumstances, but they typically do not provide information on longer term or functional outcomes. They are useful in serving as demonstration projects, yielding initial evidence that an intervention merits further study, and, in the clinical environment, they can be useful in identifying whether a particular approach to treatment is likely to be helpful for a specific child. Our goal was to identify and review the best evidence for assessing the efficacy and effectiveness of therapies for children with ASD, with an eye toward their utility in the clinical setting, and for the larger population

of children with ASD. By definition, “populations” in single-subject design studies are likely to be idiosyncratic and therefore not to provide information that is generalizable.

Nonetheless, even in studies with a comparison group, sample size is frequently insufficient to draw conclusions, and larger, multisite trials are needed across all treatment types. Furthermore, the choice of comparison groups in the studies that employed a group design was uneven. A number of studies used comparison groups that were inappropriate for observing group differences in treatment effect (e.g., comparing treatment in children with autism to the effects of the treatment in typically developing peers or to children with a different developmental disorder), and for those studies we could only use the pre-post case series data available in the group with autism, limiting the ability to comment on effectiveness.

We encourage investigators to provide adequate detail as they describe their interventions to allow for replicable research. In ideal circumstances, investigators publish and reference treatment manuals, but many studies made general references to their use of an underlying approach (e.g., ABA) without specifying the ways in which they used the technique or modifications they made to the original, published use of it. Lack of detail about the intervention makes it difficult to assess the applicability of individual studies, to synthesize groups of studies or to replicate studies.

Characterization of the study population was often inadequate, with 125 of 159 studies failing to use or report “gold standard” diagnostic measures (clinical DSM-IV-based diagnosis plus ADI-R and/or ADOS) for the participants. Because ASDs are spectrum disorders, it is difficult to assess the applicability of interventions when the population in which they were studied is poorly defined or described. Authors often do not consider diagnostic criteria in selecting participants for their studies; nor do they fully describe the children who do participate. We recommend that investigators fully describe participants in their study, both diagnostically and otherwise. In addition, because the myriad causes of ASDs are unknown, even children with the same diagnosis may have distinct genetic or other “causes” that could affect treatment effectiveness. Ideally, future research will better characterize participants genotypically and phenotypically.

We identified more than 100 distinct outcome measures used in this literature base, not accounting for subscales. The use of so many and such disparate outcome measures makes it nearly impossible to synthesize the effectiveness of the interventions, and we recommend a consistent set of rigorously evaluated outcome measures specific to each intended target of treatment to move

comparative effectiveness research forward and to provide a sense of expected outcomes of the interventions. At the same time, the means for assessing outcomes should include increased focus on use of observers or reporters masked to the intervention status of the participant, and where some outcomes are measured in a masked fashion but others not, more emphasis should be placed on those that are.

There also was a strong tendency for authors to present data on numerous outcomes without adjusting for multiple comparisons, and to fail to report the outcome that was the primary outcome of *a priori* interest and on which sample size calculations were based (when they were present). This may suggest a level of selective reporting bias in which results are published on a select group of outcomes that show the most effect. We attempted, but were unable, to identify a clear primary intended outcome in almost all of the papers.

Duration of treatment and follow up was generally short, with few studies providing data on long-term outcomes after cessation of treatment. Future studies should extend the follow up period and assess the degree to which outcomes are durable. Few studies adequately accounted for concomitant interventions that might confound observed effectiveness and this should be standardized in future research. (Warren, 2011, p. 124-125)

[Evidence Source]

Maglione (2012)

Surveillance of the literature pertaining to the Warren report was conducted by AHRQ in January 2012 and October 2012 (Maglione, 2012). Conclusions pertaining to ABA therapies that address the currency of the 2011 report are presented below:

- Original conclusions regarding low strength of evidence for Early Intensive Behavioral Interventions (EIBI) are possibly out of date due to new RCTs and long-term follow-up of previously included studies.
- Original conclusion regarding insufficient evidence for parent training is possibly out of date due to several new RCTs.
- For Key Question 2 [what are the modifiers of outcome for different treatments or approaches (frequency, duration or intensity of treatment, characteristics of child or family, training of therapy provider)], conclusions are still valid, with the exception of impact of provider type, which may possibly be out of date. (p. ii)

[Evidence Source]

AHRQ Draft Report Update (2014)

Given this evidence of additional research, AHRQ elected to update the Warren report, focusing only on behavioral interventions. They published their draft report in January 2014. A summary of the findings is below:

> We included 51 unique studies comprising 37 randomized trials and 14 nonrandomized, comparative studies (16 good, 31 fair, and 4 poor quality) published since the prior review. The quality of studies improved compared with that reported in the earlier review. Young children receiving high intensity applied behavior analysis-based early intervention over extended time frames commonly displayed substantial improvement in cognitive functioning and language skills relative to community controls. The magnitude of these effects varied across studies, potentially reflecting poorly understood modifying characteristics related to subgroups of children. Early intensive parent training programs modified parenting behaviors during interactions; however, data were more limited about their ability to improve developmental skills beyond language gains for some children. Social skills interventions varied in scope and intensity and showed some positive effects on social behaviors for older children in small studies. Evidence for play/interaction-based approaches suggested that joint attention interventions may be useful for young and preschool children with ASD when targeting joint attention skills; data on the effects of such interventions in other areas were limited. (AHRQ draft, 2014, p. v)

Of the 51 included studies, 25 addressed interventions included in this report (EIBI except when delivered as an educational intervention, symbolic play and joint attention interventions, parent training). Three studies addressed EIBI, 12 studies addressed parent training, nine studies addressed play and/or interaction based approaches and one evaluated the addition of parent training to individuals using risperidone. Some characteristics of the included studies are reported in the table below:

Table 2 Summary of new studies from AHRQ draft report update

Intervention Type	Intensity Range	Duration Range	Age Range
EIBI (excluding educational interventions)	15 to 26 hours/week[2]	24 months	15 to 54 months
Parent training	30 minutes sessions X 10 to 30	12 weeks to 2 years	18 to 66 months

[2] The study with 15 hours included an additional 16 hours of parent delivered treatment

Intervention Type	Intensity Range	Duration Range	Age Range
	hours/week home based ABA[3]		
Play/Interaction Based Interventions[4]	20 minutes 2X/day, 5 days/week to 3 hours/week[5]	6 to 12 weeks	21 to 82 months
Parent Training in addition to Risperidone	11 sessions + boosters, 1 home visit	16 weeks	4 to 14 years

With regard to the impact of intensity or duration on treatment effectiveness, the authors report the following:

- In a retrospective cohort study of EIBI, treatment duration was not determined to be a significant predictor of outcome after controlling for other variables.
- In one parent training RCT evaluating ESDM (12 one hour sessions plus treatment as usual), total intervention hours (range zero to 16 hours/week, mean 1.5 hours/week for intervention group vs. 3.7 hours/ week for control) were associated with improved developmental and vocabulary scores, as was younger child age.

With regard to strength of the evidence, the authors reach the following conclusions:

> A growing evidence base suggests that children receiving early intensive behavioral and developmental interventions (e.g., many hours of intervention a week over the course of 1-2 years) show substantial improvements in cognitive and language skills over time compared with children receiving low-intensity interventions, community controls, and eclectic non-ABA based intervention approaches. With this growing literature, our confidence (strength of evidence) in the effects of ABA-based early intensive approaches on cognitive and language outcomes is moderate, based on the need for additional research that identifies which groups of children benefit the most from specific high intensity approaches.

[3] The study that included 30 hours/week of home based ABA compared this group to three other interventions: special ed classroom (mean 13 hours/week), low-intensity, home based manualized intervention (mean 8 hours/week) and 1:1 behavioral intervention that included a 5 day parent training component (mean 13 hours/week). This study found no significant differences in cognitive or adaptive scores between groups, but did find differences in educational outcomes favoring the intensive ABA group.
[4] Typically delivered in addition to other treatment as usual
[5] Four of the studies did not report treatment intensity

Our strength of evidence in these high intensity interventions to affect adaptive behavior skills, social skills, and core ASD symptom severity is low. At present it is challenging to understand which high intensity variants most robustly impact these domains for specific children and in general the impact of these skill domains is less consistent.

A growing evidence base suggests that children receiving early joint attention-related intervention in combination with other interventions show substantial improvements in joint attention and language skills over time. Within this growing literature, our confidence (strength of evidence) in this effect is moderate, based on the need for additional research that identifies which groups of children benefit the most from this approach and how this intervention relates to other ongoing concurrent offered interventions. Results from a variety of play-based interventions also suggest that young children often display short-term improvements in early play, imitation, language, and social interaction skills. However, our confidence in these estimates is low, and substantial evidence that these short-term improvements are linked to broader indices of change over time is lacking (AHRQ draft, p. 75).

The evidence base for parent training interventions is moderate for their impact on early language and communication skills and low for impact on ASD symptom severity and early cognition. There is not yet sufficient data from this literature base to understand impact on adaptive behavior skills. Available studies indicate variable responses, with modest improvement for some children in some approaches, but limited improvement in other parent training paradigms. (AHRQ draft, 2014, p. 67)

Parent-mediated Early Intervention

Oono (2013)

A review of parent-mediated early intervention in children less than seven was completed by the Cochrane Collaboration in April 2013 (Oono, 2013). It included 17 RCTs (one of which was identified in the AHRQ surveillance report, and eight of which were included in the original Warren report) and drew the following conclusions:

Overall, we did not find statistical evidence of gains from parent-mediated approaches in most of the primary outcomes assessed (most aspects of language and communication - whether directly assessed or reported; frequency of child initiations in observed parent-child interaction; child adaptive behaviour; parents' stress), with findings largely inconclusive and inconsistent across studies. However, the evidence for positive change in patterns of parent-child interaction was strong and statistically significant (shared attention: standardized mean difference (SMD) 0.41; 95% confidence interval (CI) 0.14 to 0.68, P value <

> 0.05; parent synchrony: SMD 0.90; 95% CI 0.56 to 1.23, P value < 0.05). Furthermore, there is some evidence suggestive of improvement in child language comprehension, reported by parents (vocabulary comprehension: mean difference (MD 36.26; 95% CI 1.31 to 71.20, P value < 0.05). In addition, there was evidence suggesting a reduction in the severity of children's autism characteristics (SMD -0.30, 95% CI -0.52 to -0.08, P value < 0.05). However, this evidence of change in children's skills and difficulties as a consequence of parent-mediated intervention is uncertain, with small effect sizes and wide CIs, and the conclusions are likely to change with future publication of high-quality RCTs. (Oono, 2013, p. 2)

This conclusion differs from that of the AHRQ draft report, for unclear reasons. It may be because Oono 2013 limited their population to children less than seven, or it may be that the AHRQ draft included more recent studies, since there is nearly a year difference in the literature search end dates (July 2013 for the AHRQ draft and August 2012 for Oono 2013). It also may be variable interpretation of the strength of the evidence by different authors. Indeed, the Oono 2013 review does find a statistically significant benefit in language comprehension and autism severity, outcomes that the AHRQ draft authors assess as having moderate and low strength of evidence respectively. However, Oono 2013 downgrades these findings because they are based on parent self report, and have small effect sizes and wide confidence intervals.

[Evidence Source]

Adolescents and Young Adults (Ages 13 to 30)

Lounds (2012)

Only one poor quality case series evaluated ABA-based intensive behavioral therapy, precluding conclusions regarding efficacy in this age group (Lounds, 2012).

[Evidence Source]

Evidence Summary

Based on the evidence presented in this document (Warren, 2011; AHRQ draft, 2014; Oono, 2013), there is moderate strength of evidence that EIBI improves cognitive and language skills, and low strength of evidence that EIBI improves adaptive behavior skills, social skills, and core symptoms of autism, although improvements are inconsistent. Parent-mediated early intervention improves early language and communication skills, including shared attention and parent synchrony (moderate strength of evidence), and may have some impact on autism symptom severity and early cognition (low strength of evidence). Play-/interaction-based interventions improve child joint attention and language skills (moderate strength of evidence) and play, imitation and social interaction skills (low strength of evidence). The evidence is insufficient to evaluate the effectiveness of ABA on children and adolescents older than twelve. The evidence is insufficient to determine whether there are any factors that modify the effectiveness of ABA therapy.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/Intervention	Balance between desirable and undesirable effects	Quality of evidence	Resource allocation	Values and preferences	Recommendation
Children aged 1 to 12 years at initiation					
Early Intensive Behavioral Interventions	Benefit on cognitive and language skills	Moderate	High	Low variability	Recommendation for coverage (strong recommendation)
	Benefit on adaptive behavior, social skills and overall autism severity	Low	High	Low variability	
Parent training interventions	Increased joint attention and parent synchrony, and improved early language and communication skills	Moderate	Moderate	Low variability	Recommendation for coverage (strong recommendation)
	Lessened overall severity of autism and improved early cognition	Low	Moderate	Low variability	
Play/interaction-based interventions (including joint attention interventions)	Improvements in joint attention and language skills	Moderate	Low	Low variability	Recommendation for coverage (strong recommendation)
	Short-term improvements in play, imitation, social skills	Low	Low	Low variability	
Adolescents and young adults					
ABA	Unknown	Insufficient	Moderate for focused, high	Low variability	Recommend noncoverage of

Indication/Intervention	Balance between desirable and undesirable effects	Quality of evidence	Resource allocation	Values and preferences	Recommendation
			for more comprehensive		intensive ABA therapies *(weak recommendation)* Recommendation for coverage for specific problem behaviors with focused interventions *(weak recommendation)*

Note: GRADE framework elements are described in Appendix A

SUMMARY CONCLUSIONS

Children ages 1 to 12

Applied behavior analysis (ABA), including early intensive behavioral intervention (EIBI), is recommended for coverage[6] for treatment of autism spectrum disorder[7] (*strong recommendation*).

> Rationale: This strength of recommendation was based on sufficient (moderate quality) evidence and expert input, including testimony on parent/caregiver values and preferences.

Specifically, EIBI (for example, UCLA/Lovaas or ESDM), is recommended for coverage for up to 25 hours per week for a maximum of three years.

> Rationale: The 25-hour limit would be similar to other payers in Oregon that were mandated through SB 365 and earlier Warren report had demonstrated 25 hours per week was effective. There is no evidence that increased intensity beyond this level yields improves outcomes. The duration limit is based on the fact that EIBI studies have a duration of 2-3 years

Initial coverage of EIBI should be provided for up to six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using standardized, multimodal assessments, no more frequently than every six months *(strong recommendation).* Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).

> Rationale: Ensuring that patients are making meaningful progress is important to ensure quality outcomes and effective use of resources. The six month assessment was chosen based on expert input and subcommittee deliberation to allow for sufficient time for progress while not being burdensome to providers and plans.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive behavioral ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions)

[6] These conclusions apply to the Oregon Health Plan as governed by the Prioritized List of Health Services and to no other health plan.
[7] Autism spectrum disorder should be diagnosed by a qualified health care professional according to DSM-5 criteria.

are recommended for coverage to address core symptoms of autism and/or specific problem areas *(strong recommendation)* for up to 8 hours per month. In extenuating circumstances (e.g severe aggressive behavior that is responding to interventions but requires increased intensity), an additional 8 hours per month is recommended for coverage. Initial coverage should be provided for six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives or emergence of new problem behaviors.

> Rationale: Not all autistic children require comprehensive therapy and less intensive interventions will be appropriate for many, or appropriate for those who have completed intensive intervention. Evidence supports these less intensive interventions in this age group. Eight hours was chosen based on a wide range of intensity in the literature, expert input, and previous HERC Prioritized List guideline precedent.

Parent/caregiver involvement and training is recommended to be a component of treatment *(strong recommendation)*.

> Rationale: Evidence and expert input indicated that parental involvement in ABA is a key part of effective treatment. Parent delivered therapy is effective.

Individuals ages 13 and older

Intensive ABA is not recommended for coverage for treatment of autism spectrum disorder in persons ages 13 and older (*weak recommendation*).

> Rationale: There is insufficient evidence to support intensive ABA treatment at older ages.

For individuals age 13 and older, targeted behavioral interventions, including focused ABA*, are recommended for coverage for up to 8 hours per month, up to 6 months, only to address specific problem behaviors (*weak recommendation*). Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. The interventions should involve predefined behavioral objectives that would result in socially important and sustainable outcomes for the individual. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives with ongoing proof of medical appropriateness, or emergence of new problem behaviors.

Rationale: According to the trusted evidence source, there is insufficient evidence to support ABA-based interventions in this age group. Public comment and some expert testimony involved submission of many single subject research design studies to support treatment in this age group, but the quality of this evidence did not meet predetermined criteria for inclusion. The subcommittee agreed that problem behaviors can be challenging to the individual, caregivers, and society and it is reasonable to consider targeted interventions for specific problem behaviors as long as there are clear objectives, progress toward meaningful predefined goals and ongoing proof of medical appropriateness. The net result was to recommend targeted interventions including ABA-based treatments for limited intensity to address problem behaviors. Six months was chosen based on expert testimony and subcommittee discussion that more frequent assessments would potentially be burdensome to providers and plans.

Parent/caregiver involvement and training is encouraged *(weak recommendation)*

Note: The evidence for the treatment of conditions comorbid with autism spectrum disorder is beyond the scope of this evidence summary.

POLICY LANDSCAPE

No quality measures were identified when searching the National Quality Measures Clearinghouse pertaining to autism and applied behavioral analysis.

COMMITTEE DELIBERATIONS – EVIDENCE-BASED GUIDELINES SUBCOMMITTEE

COMMITTEE DELIBERATIONS – VALUE-BASED BENEFITS SUBCOMMITTEE

This report is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide HERC in making informed decisions about the prioritization of health care services for the Oregon Health Plan.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Appendix B. Potentially Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
299.00	Autistic disorder, current or active state
299.01	Autistic disorder, residual state
299.10	Childhood disintegrative disorder, current or active state
299.11	Childhood disintegrative disorder, residual state
299.80	Other specified pervasive developmental disorders, current or active state
299.81	Other specified pervasive developmental disorders, residual state
299.90	Unspecified pervasive developmental disorder, current or active state
299.91	Unspecified pervasive developmental disorder, residual state
ICD-10 Diagnosis Codes	
F84.0	Autistic disorder
F84.2	Rett's syndrome
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
ICD-9 Volume 3 (Procedure Codes)	
None	
Procedure Codes	
Until July, 2014, no specific procedure codes exist for Applied Behavior Analysis. The list below provides examples of how various state Medicaid agencies covering ABA instruct providers to bill. Temporary codes shown in italics will be available starting July, 2014.	
90834	Psychotherapy, 45 min
90837	Psychotherapy, 60 min
0359T	*Behavior identification assessment, by the physician or other qualified health care professional, face-to-face with patient and caregiver(s), includes administration of standardized and non-standardized tests, detailed behavioral history, patient observation and caregiver interview, interpretation of test results, discussion of findings and recommendations with the primary guardian(s)/caregiver(s), and preparation of report*
0360T	*Observational behavioral follow-up assessment, includes physician or other qualified health care professional direction with interpretation and report, administered by one technician; first 30 minutes of technician time, face-to-face with the patient*
0361T	*…additional 30 minutes*
0362T	*Exposure behavioral follow-up assessment, includes physician or other qualified health care professional direction with interpretation and report, administered by physician or other qualified health care professional with the assistance of one or more technicians; first 30 minutes of technician(s) time, face-to-face with the patient*
0363T	*… additional 30 minutes*
0364T	*Adaptive behavior treatment by protocol, administered by technician, face-to-face with one patient; first 30 minutes of technician time*
0365T	*…additional 30 minutes*

CODES	DESCRIPTION
0366T	*Group adaptive behavior treatment by protocol, administered by technician, face-to-face with two or more patients; first 30 minutes of technician time*
0367T	*….additional 30 minutes*
0368T	*Adaptive behavior treatment with protocol modification administered by physician or other qualified health care professional with one patient; first 30 minutes of patient face-to- face time*
0369T	*Adaptive behavior treatment with protocol modification, additional 30 minutes*
0370T	*Family adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present)*
0371T	*Multiple-family group adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present)*
0372T	*Adaptive behavior treatment social skills group, administered by physician or other qualified health care professional face-to-face with multiple patients*
0373T	*Exposure adaptive behavior treatment with protocol modification requiring two or more technicians for severe maladaptive behavior(s); first 60 minutes of technicians' time, face-to-face with patient*
0374T	*each additional 30 minutes of technicians' time face-to-face with patient (List separately in addition to code for primary procedure)*
G1076	Activity therapy, such as music, dance, art or play not for recreation, related to the care and treatment of patient's disabling mental health problems (45 min or more)
G1077	Training and educational services related to the care and treatment of patient's disabling mental health problems (45 min or more)
H0002	Behavioral health screening to determine eligibility for admission to treatment program
H0004	Behavioral health counseling and therapy, per 15 minutes
H0031	Mental health assessment by non-physician
H0032	Mental health service plan development by non-physician
H2000	Comprehensive multidisciplinary evaluation
H2010	Comprehensive medication services, per 15 minutes
H2019	Therapeutic behavioral service, per 15 minutes
H2020	Therapeutic behavioral service, per diem
H2027	Psychoeducational service, per 15 min
T1023	Screening to determine the appropriateness of consideration of an individual for participation in a specified program, project or treatment protocol, per encounter
T1024	Evaluation and treatment by an integrated, specialty team contracted to provide coordinated care to multiple or severely handicapped children, per encounter
T1027	Family training and counseling for child development, per 15 min
T2013	Habilitation, educational, waiver, per hour
T2026	Specialized childcare, waiver, per diem

Note: Inclusion on this list does not guarantee coverage

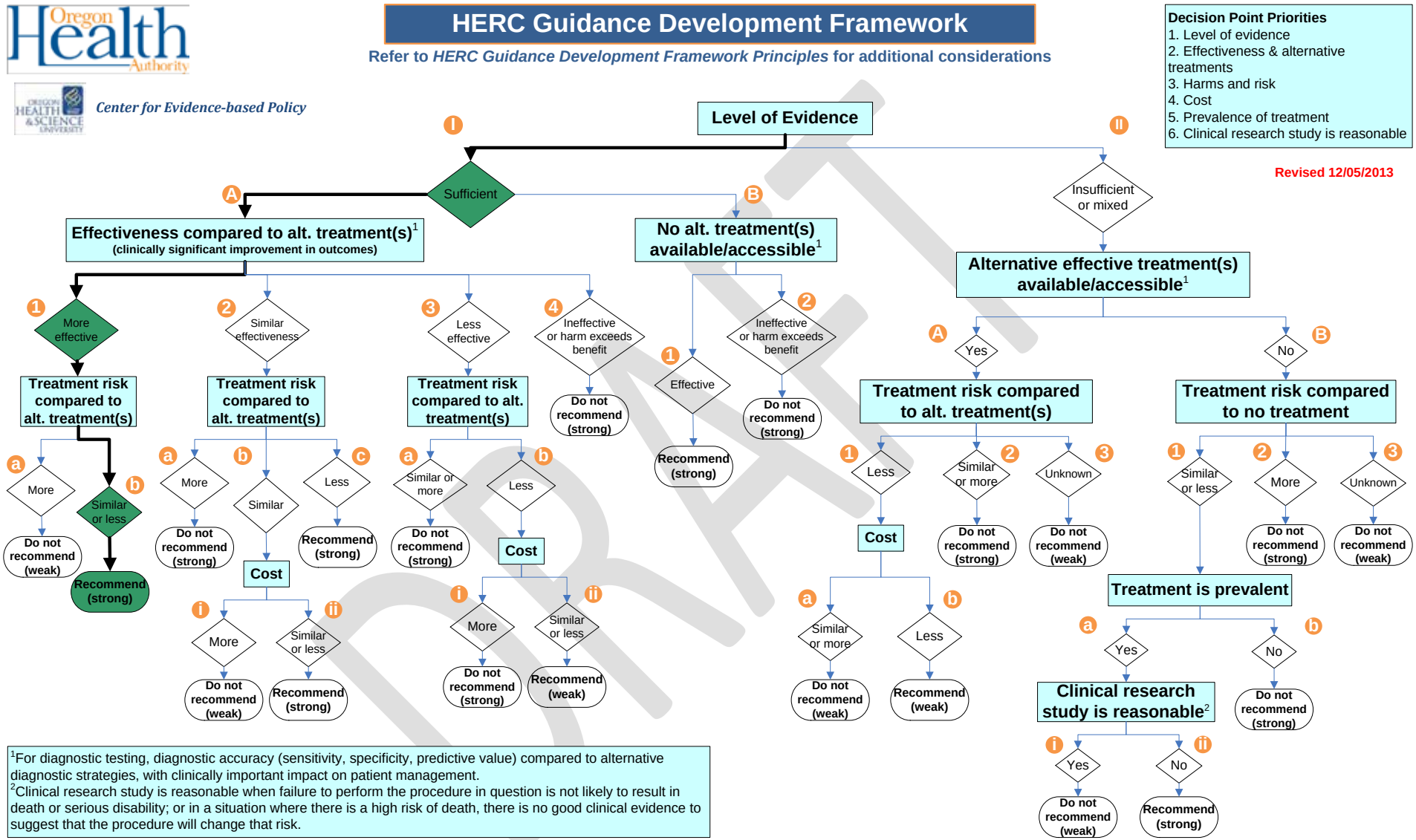
Appendix C. HERC Guidance Development Framework

HERC Guidance Development Framework Principles

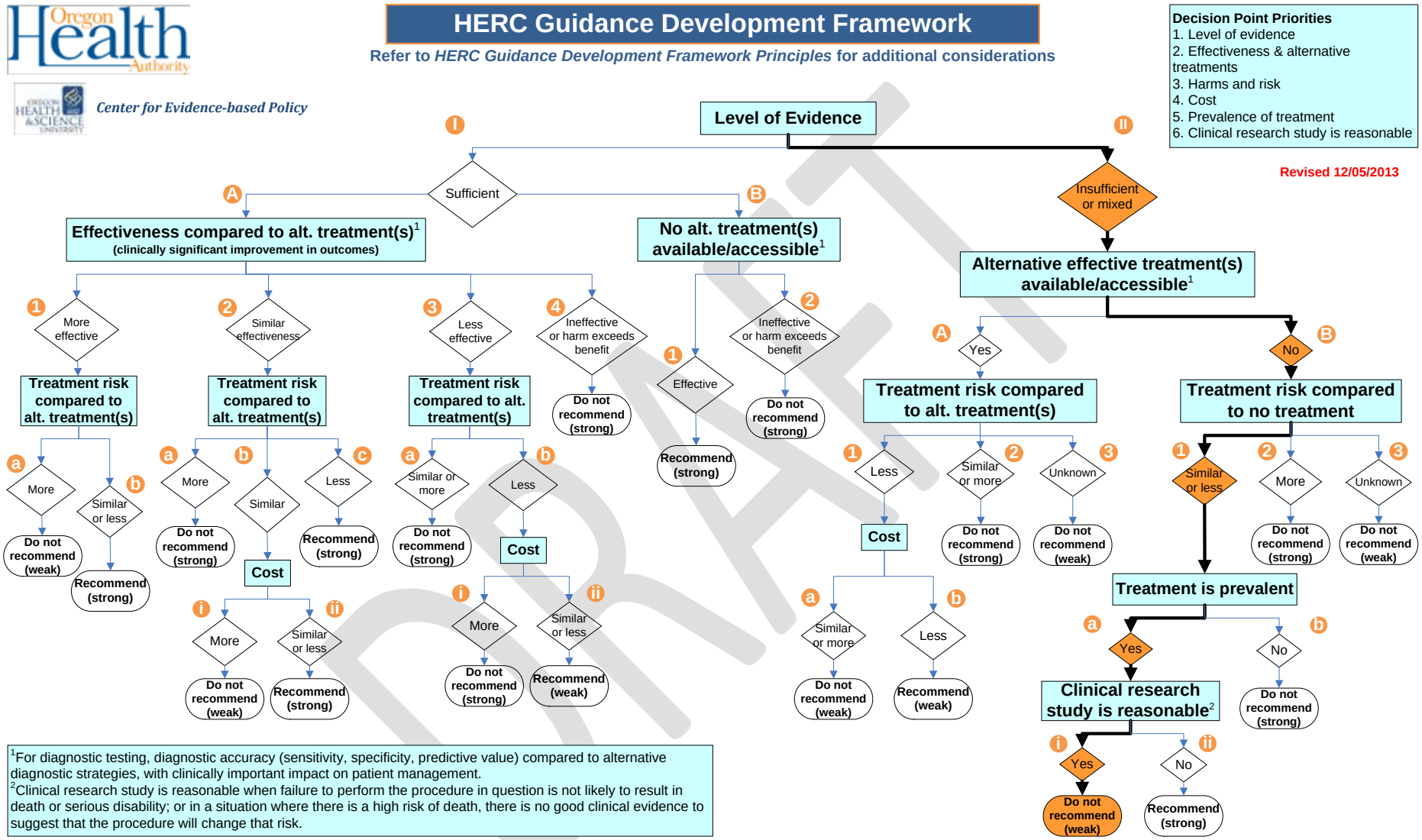
This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients

ABABA-based Treatments for Children Aged 1 to 12, including EIBI and Other Less Intensive Interventions



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
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Appendix D. Key References from Evidence Sources

References for Included Studies in Oono 2013

Aldred C, Green J, Adams C. A new social communication intervention for children with autism: pilot randomised controlled study suggesting effectiveness. *Journal of Child Psychology and Psychiatry* 2004;45(8):1420–30. *{published data only}*

Carter AS, Messinger DS, Stone WL, Celimli S, Nahmias AS, Yoder P. A randomised controlled trial of Hanen's "More Than Words" in toddlers with early autism symptoms. *Journal of Child Psychology and Psychiatry* 2011;52(7):741- 52. *{published data only}*

Casenhiser DM, Shanker SG, Stieben J. Learning through interaction in children with autism: preliminary data from a social-communication-based intervention. *Autism* 2013; 17(2):220–41. *{published data only}*

Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized controlled trial of an intervention for toddlers with autism: the Early Start Denver M model. *American Academy of Pediatrics: Pediatrics* 2010;125(1):e17–23. *{published data only}*

Drew A, Baird G, Baron-Cohen S, Cox A, Slonims V, Wheelwright S, et al. A pilot randomised controlled trial of a parent training intervention for pre-school children with autism. *European Child and Adolescent Psychiatry* 2002;11 (6):266–72. *{published and unpublished data}*

Green J, Charman T, McConachie H, Aldred C, Slonims V, Howlin P, et al. Parent-mediated communication-focused treatment in children with autism (PACT): a randomised controlled trial. *Lancet* 2010;375(9732):2152–60. *{published data only}*

Jocelyn LJ, Casiro OG, Beattie D, Bow J, Kneisz J. Treatment of children with autism: a randomised controlled trial to evaluate a caregiver-based intervention program in community day-care centres. *Journal of Developmental & Behavioral Pediatrics* 1998;19(5):326–34. *{published data only}*

Kasari C, Gulsrud AC, Wong C, Kwon S, Locke J. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. *Journal of Autism and Developmental Disorders* 2010;40(8):1045-56. *{published data only}*

Nefdt N, Koegel R, Singer G, Gerber M. The use of a self- directed learning program to provide introductory training in pivotal response treatment to parents of children

with autism. *Journal of Positive Behavior Interventions* 2010;12 (1):23–32. *{published data only}*

Pajareya K, Nopmaneejumruslers K. A pilot randomised controlled trial of DIR/Floortime™ parent training intervention for pre-school children with autistic spectrum disorders. *Autism* 2011;15(5):563-77. *{published data only}*

Rickards AL, Walstab JE, Wright-Rossi RA, Simpson J, Reddihough DS. A randomised controlled trial of a home- based intervention program for children with autism and developmental delay. *Journal of Developmental and Behavioral Pediatrics* 2007;28(4):308–16. *{published data only}*

Roberts J, Williams K, Carter M, Evans D, Parmenter T, Silove N, et al. A randomised controlled trial of two early intervention programs for young children with autism: centre-based with parent program and home-based. *Research in Autism Spectrum Disorders* 2011;5(4):1553-66. *{published data only}*

Siller M. A parent-mediated intervention to increase responsive parental behaviors and child communication in children with ASD: a randomized clinical trial. Journal of Autism and Developmental Disorders 2012. *{published data only}*

Silva LTM, Schalock M, Ayres R, Bunse C, Budden S. Qigong massage treatment for sensory and self-regulation problems in young children with autism: a randomized controlled trial. *American Journal of Occupational Therapy* 2009;63(4):423-32. *{published data only}*

Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. *American Journal on Mental Retardation* 2000;105(4):269–85. *{published data only}*

Tonge B, Brereton A, Kiomall M, Mackinnon A, King N, Rinehart N. Effects on parental mental health of an education and skills training program for parents of young children with autism: a randomised controlled trial. *American Academy of Child and Adolescent Psychiatry* 2006; 45(5):561–9. *{published data only}*

Wong VCN, Kwan QK. Randomized controlled trial for early intervention for autism: a pilot study of the Autism 1- 2-3 Project. *Journal of Autism and Developmental Disorders* 2010;40(6):677-88. *{published data only}*

HERC Evidence Evaluation – Applied Behavior Analysis for Autism Spectrum Disorders
Disposition of Public Comments

Table of Contents

Commenters

Identification	Stakeholder
A	CCO Medical Directors, *Oregon*
B	Board Certified Behavior Analyst, *Portland, OR*
C	Trillium Family Services, *Portland, OR*
D	Care Manager (Pediatrics), *Clackamas, OR*
E	Parent of child with autism, *Tualatin, OR*
F	Residential Associate at adult care facility, *Portland, OR*
G	Developmental Pediatrician, Eugene Regional Service Center, *Eugene, OR*
H	Autism Society of Oregon, *Marylhurst, OR*
I	Family member of autistic person, *Portland, OR*
J	Family member of autistic person, *Portland, OR*
K	Family member of autistic person, *Portland, OR*
L	Family member of autistic person, *Portland, OR*
M	The Lovaas Institute for Early Intervention, *Minneapolis, MN* *Submitted by Eric V. Larsson, Ph.D., L.P., B.C.B.A.-D. – HERC-appointed Expert*
N	Licensed psychologist, Professor of Pediatrics, Oregon Health & Science University, *Portland, OR*
O	Licensed psychologist
P	Autism Speaks, *Boston, MA*
Q	A Hope for Autism Foundation, *Portland, OR*
R	Parent of child with autism, *Fort Collins, CO*
S	Parent of child with autism, *Portland, OR*
T	Family member of autistic person, *Portland, OR*

U	Parent of child with autism, *Salem, OR*
V	Association of Professional Behavior Analysts, *San Diego, CA* *Submitted by Gina Green, PhD, BCBA-D – HERC-invited Presenter*
W	Former manager of Wylie Center Autism Spectrum Intervention Program, *Riverside, California*
X	Family member of autistic person, *Bend, OR*
Y	Oregon Association for Behavior Analysis Board (ORABA) Board, *Bend, OR*
Z	Attorney, *Portland, OR*
AA	Family member of autistic person, *Portland, OR*
BB	Associate Professor and Program Director of School Psychology at the University of Oregon, *Eugene, OR*

Public Comments Grouped by Commenter

Ident.	#	Comment	Disposition
A	1	• We are concerned about who makes the diagnosis of autism in order to qualify for ABA (schools versus medical professionals). Consider adding language requiring diagnosis to be based on a medical professional assessment using DSM V criteria. • There should be an upper limit on ABA. • Were electronic and high tech options considered in the evidence review?	The focus of this evidence evaluation is limited to treatment of ASD, specifically, ABA therapy. Language stating that ASD should be diagnosed by a qualified healthcare professional according to DSM-5 criteria is present in the summary conclusions of the evidence evaluation. Assuming commenter is referring to number of hours per week when suggesting an upper limit on ABA, the evidence included interventions that ranged from less than 2 to 40 hours per week, and no minimum or maximum has been determined to be required for efficacy. Electronic options (including such treatments as Picture Exchange Communication System (PECS) are addressed in the source report, but are not included in this document because they are not considered ABA.
B	1	I am writing to encourage support for Applied Behavior Analysis (ABA) services for persons ages 12 and older with developmental disabilities. I am a Board Certified Behavior Analyst working with individuals 8 years and older in the Portland area. I work with this age range because there is a great need for behavioral support services for adolescents and adults with disabilities. I regularly receive calls from families whose adolescent or adult children are not getting their needs met through the existing educational and cultural systems.	Thank you for taking the time to comment.
B	2	Many existing services for persons with developmental disabilities focus on early intervention therapy, and specialized services for adolescents and adults can be hard to find. But adulthood is a hugely important time in a person's life that presents its own unique challenges. It is in adulthood that one is expected to have the most access and control over the variables that affect an individuals quality of life – friends, hobbies, jobs, and living space. Quality of life for adults with disabilities is below that of the non-disabled population. *"Of all working-age people with disabilities, only 21% say that they are employed, compared to 59% of people without disabilities – a gap of 38 percentage points. People with disabilities are still much more likely to be living in poverty. People with disabilities are less likely than those without disabilities to*	EbGS understands the difficulties experienced by the adult disabled population. Other services besides ABA are currently covered by the OHP for individuals with developmental disabilities (guideline note 75).

Ident.	#	Comment	Disposition
		socialize with friends, relatives or neighbors, once again suggesting that there are significant barriers to participation in leisure activities for this population. (National Organization on Disability, 2010)" National Organization on Disability. (2010). *2010 NOD/Harris survey of Americans with disabilities.* http://www.2010DisabilitySurveys.org/indexold.html	
B	3	ABA is a behavioral science that, by definition, focuses on problems of social importance. It has over 35-years of peer-reviewed research on improving the quality of life of individuals with and without disabilities. As more and more children age out of the education system, they will need supports to help them address the new challenges they will face as adults. To set an individual up for success, this type of transition planning has to start in adolescence. I have provided ABA services to several adolescents and adults. Here is a list of some of the skills they have needed help with: learning to navigate the trimet bus system independently, practicing social safety skills like what to do when lost, using money and making smart decisions about purchases, learning to identify abusive and unhealthy relationships, learning and practicing appropriate sexual behavior, and accessing community resources. My clients mastered these skills as a result of the ABA therapy provided. Some of these skills are not appropriate to teach before the age of 12, but are absolutely essential skills to have as an adult. While some individuals may learn these skills through school and through family, others need the help of a behavior specialist. Please support ABA for adolescents and adults with disabilities, and help those that need it most to get the skills they need for a higher quality of life. Thank you for your consideration.	EbGS appreciates the need for development of the skills described by the commenter, however, the effectiveness of ABA in developing those skills in children older than 12 is not supported by the evidence.
C	1	Please consider this message a strong recommendation from Trillium Family Services to include Applied Behavior Analysis (ABA) on the prioritized list of treatments in the Oregon Health Plan (OHP). Trillium is Oregon's largest provider of mental and behavioral health services for children and families. We have long contended that for many of those we serve – and countless others in our state – there exists a glaring and unacceptable lack of treatment for children on the autism spectrum. Three years ago, Trillium made a significant investment in exploring whether programs could be developed for this greatly underserved population. While we found the need in our communities and for our families was significant, we were forced to abandon the plan because no funding mechanisms existed through either the OHP or the commercial health insurance market to make the provision of these services feasible. During this process, however, we did conclude that ABA was a successful and effective evidence-based model in treating autistic children. More recently, we have developed a partnership with Footprints Behavioral Interventions to provide assessment and diagnostic services and deliver ABA therapy to children and young adults in Oregon ranging in age from 2 to 20 years old. We are nearing an agreement with Kaiser Permanente to fund	Thank you for sharing the background on your organization.

Ident.	#	Comment	Disposition
		these services, which would thus be available only to its members. We anticipate, however, that other commercial insurance companies in Oregon will begin providing similar coverage in the near future.	
C	2	We believe these services will result in higher functioning of clients within their families, schools and communities, greater independence and job readiness, and ultimately reduced health care costs. **These outcomes could be similarly achieved for those covered under the OHP.** As such, we support HERC's recommendation in favor of ABA coverage for younger children covered by the OHP; we believe the quality of evidence should be revised to Medium or High; and we believe there should be no minimum age for accessing ABA therapy.	The commenter does not provide additional evidence to support their contention that the quality of evidence for ABA is moderate to high, or that it is effective for children younger than two.
C	3	Further, we believe there is sufficient evidence to support the effectiveness of ABA for patients over the age of 12, and that coverage should be provided when medically necessary. A lack of treatment for those with severe symptoms may lead to self-injurious behaviors causing severe disabilities. **Please include Applied Behavior Analysis therapy on the prioritized list of treatments in the Oregon Health Plan.**	The commenter does not provide evidence for the effectiveness of ABA in children over age 12. The evidence reviewed by the EbGS does not support its use.
D	1	I am very excited to see you speak of ABA coverage! I am all in favor of autistic kids ages 2-12 getting ABA for a period of 6 months. Please keep me posted on any current happening.	Thank you for taking the time to comment.
E	1	I am writing to comment on access to ABA therapy as a prioritized treatment in the Oregon Health Plan. My child is severely impacted by Autism, and has been referred clinicians for ABA therapy on several different occasions. Because we cannot afford the therapy in addition to the other out of pocket costs associated with raising our child, and because our insurance provider has denied coverage on several different occasions, my son has not benefitted from ABA except through a program that is administered through the local education service district. Unfortunately, that service is only provided four days a week for an hour at a time. I'm having a hard time considering why Oregon would not want to cover ABA therapy for children immediately upon diagnosis. First and foremost, the people referring parents of autistic children to ABA therapy are professional doctors, clinicians, and specialists. Why question the experts? What do they have to gain by trying to enrich a childs life. Please approve coverage or access to ABA therapy within the OHP. There are plenty of children on the spectrum that do not have the resources available to get the help they need to foster a full and productive life from their children. I always believe that we can choose to pay now, and hope for the best results, or concede to the disease, and pay later housing and taking care of these children and young adults who did not have every opportunity available provided to them. Thank you for your time. If you have any questions please contact me.	Thank you for taking the time to comment. While experts are generally well-intentioned, there are many examples in the history of medicine of experts being proved wrong by a well-designed research study, hence the EbGS's focus on clinical research. The current evidence evaluation **does** recommend OHP coverage of ABA for children 2 to 12 with ASD.
F	1	I feel it worthwhile and necessary to provide feedback to the Oregon Health Evidence Review Commission on some of the issues concerning the recent publication of the draft of the Evaluation of Evidence for Applied Behavior Analysis (ABA) treatment for Autism Spectrum Disorders (ASDs) which	EbGS agrees that types and intensities of services vary significantly in the studies included in the source report, and that there is difficulty in pooling this data to draw

Ident.	#	Comment	Disposition
		is to be made available to families and children diagnosed with Autism Spectrum Disorders in Oregon as a result of the passing of Senate Bill 365 earlier this year: Permit me, please, to address some concerns that arose for me in reading the ABA Evaluation of Evidence draft. I find that the review articles which are considered in the draft, particularly that by Warren and colleagues (2011), although well-intentioned to inform the public about the efficacy of ABA, suffer from a series of misunderstandings about the specific nature of ABA treatment and about how efficacy is demonstrated in determining the success of a behavioral treatment for a person. The authors don't seem to distinguish very well between types of ABA services provided to clients or between different intensities of services. They examine data for some interventions which may not be ABA-based, and have lumped ABA-based interventions of different intensities together under general labels, whereas the intensity and consistency of behavioral interventions that matches the nature of the problem, has proven to be one of the keys in producing good outcomes. Most seriously, though, these reviews base their conclusions about evidence strength on the standard of randomized controlled trial (RCT) studies. The RCT between-groups study design which is prioritized, looks at the differences in how a treatment affects the group of people to whom that treatment is provided, versus a group of individuals which receives no treatment (or a placebo). The design assumes that the purportedly random sample used for each group is representative of the entire population of interest. In presenting the summary of effects between these two groups, it does not take into close account individual differences and specific individuals in the treatment group which might have not benefited at all, or which have suffered adverse side-effects (which are then listed in a precautionary manner).	meaningful conclusions. EbGS is unable to respond to commenter regarding which interventions they do not believe are ABA based, since those interventions are not specified. EbGS agrees with the commenter's statements regarding RCTs; while it is possible for a RCT to assess subgroups, none of the studies in the Warren report were powered to do so, and RCTs do not assess individuals.
F	2	In the single-subject study design used to evaluate individualized ABA treatment, no such assumptions exist. The behavior of an individual undergoing treatment is studied in detail, an intervention is developed based on prior scientific applications of behavioral sciences combined with evidence about this individual's strengths and abilities. Experimental control that shows effect for that individual is generally demonstrated by alternation of baseline/treatment conditions and **comparison of the results of the intervention to the earlier baseline data for that same individual**. This comparison is the demonstration of effect which does not require complex statistics to ascertain and yet is much more detailed. Moreover, the fact that experimental control is demonstrated makes this study design completely distinct from a simple case study, which is the accumulation of evidence without the benefit of experimental control. The strength of evidence criteria do not seem to make this vital distinction sufficiently strongly, which is particularly troubling because each successful ABA-based treatment study using single subject design (of which there are by now thousands), constitutes scientifically valid systematic replication that adds support to ABA as an efficacious treatment method	EbGS acknowledges the distinction between single subject research design (SSRD) and case series. One of the primary problems of single subject design research is generalizability, or the likelihood that the results may apply to others. For an intervention to be considered evidence-based, Horner et al (2005) propose that the effect be replicated in at least 5 SSRD studies, that they be carried out by at least 3 different researchers in at least three different locations, and that those 5 studies include at least 20 subjects. The Warren report did include this study design as long as it included at least 10 subjects.

Ident.	#	Comment	Disposition
		for ASD specifically because of the experimental control component.	
F	3	When taken together, the issues described above are likely to present a very misleading picture of the efficacy of ABA treatment for ASD and may put severe constraints on its availability to Oregonians who are likely to benefit. Given the varied nature of the manifestations of Autism Spectrum Disorders and relevant behavior problems and skill deficits likely to exist for any given diagnosed individual, it is imperative that a treatment be individualized if it is to be successful. The excessively narrow standard of evidence favoring between-groups design, is therefore very much misapplied, as it might be in other instances where highly individualized treatment were needed, such as essential surgeries. I urge this commission, prior to finalizing the Evaluation of Evidence for ABA, to seek the input of behavior analysis professionals with the understanding of the scientific implications of single-subject study design and group-based designs other than RCT for the purpose of treatment evaluation, who also possess the nuanced knowledge of the variety of ABA-based treatment procedures across diagnoses, populations and age groups, the criteria for the applications of these methods, and the evidence for their outcomes.	EbGS does not dispute the need to individualize treatment, and is aware that this needs to be done for many conditions. SSRD studies were included in the review when they met prespecified criteria. EbGS has sought input from experts, and has appointed three experts to assist the committee.
G	1	I am writing to comment on the recently released evaluation of evidence and draft recommendations on applied behavior analysis for children and adolescents with autism. I am a Developmental Pediatrician and Professor of Pediatrics at the Institute on Development and Disability (formerly the Child Development and Rehabilitation Center), Oregon Health & science University. I have more than 30 years' experience working with children with developmental disabilities including autism spectrum disorder and their families. I support the commission's recommendation in favor of ABA for children 2 -12 years of age, however, I strongly recommend the commission reconsider the failure to recommend ABA services for children less than 2 years of age or older than 12 years of age. There should be no minimum age for ABA. The absence of more robust research data on the effectiveness of ABA therapies for children less than 2 years of age primarily reflects the age at which an accurate autism diagnosis can be made for most children. Children who do receive a definitive diagnosis prior to 2 years of age should not be denied access to the most effective therapy, ABA. I have worked for many years on a multi-disciplinary diagnostic team at CDRC and am currently working to train and support medical-educational teams for autism identification in 4 local communities. In many instances, a definitive diagnosis of an autism spectrum disorder often can be made prior to 2 years of age. These children and their families deserve prompt access to treatment services.	Thank you for taking the time to comment. EbGS agrees that there is not robust research regarding ABA in children under 2, and acknowledges this is likely because of the difficulty in arriving at a definitive diagnosis before that age. Without a diagnosis, it is problematic to prescribe treatment. In response to expert opinion, EbGS lowered the recommended age to consider treatment to one year.
G	2	There should be no limitation to ABA therapies for individuals over 12 years of age. The focus of ABA treatment for adolescents and young adults is often on challenging behaviors, for example, self-injurious behaviors. There is a wealth of information on the use of ABA techniques to successfully	See comment #F2 regarding SSRD. EbGS appreciates the desirability of treatment with behavioral therapies before the use of psychotropic medications with

Ident.	#	Comment	Disposition
		treat these issues. Data is primarily from well-designed single subject studies; however, this is supplemented with my clinical experience and that of any other health care professional who regularly treats older children and adolescents who have autism. Behavioral therapies are critical for these children. Best practice is to first provide behavioral interventions based on a careful functional analysis. In some cases this will obviate the need for psychotropic medications and their risk of potentially serious side effects. Further information on ABA and the utility of single subject research design is available through the National Autism Center and their National Standards project. I assume the commission is familiar with this resource.	significant risks, but does not believe there is sufficient evidence of effectiveness. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors. Note to EbGS: The NAC is supported by the May Institute, a non-profit organization that provides services (all based on ABA) to individuals with ASD and other disabilities, as well as providing training in ABA. NAC is the May Institute's "center for the promotion of evidence-based practice." They completed the National Standards Project (NSP) in 2009, which is described as an evidence-based guideline of treatments for ASD.
H	1	Autism Society of Oregon (ASO) is the largest autism advocacy organization in Oregon, representing the over 9,000 individuals who have an autism spectrum disorder and their families. Annually, over 6,400 people are actively involved in ASO's programs. We have volunteers and activities in every region of Oregon. Our constituents range from very young children to senior citizens, and from mildly to very significantly impacted by autism. • ASO supports HERC's draft recommendation for coverage of ABA for young children, but disagrees that the strength of evidence in support of this recommendation is "low." • ASO disagrees with HERC's draft recommendation against ABA coverage for people over age 12. We are dismayed that HERC has not followed its own processes in reaching these draft conclusions and has not considered crucial information submitted to HERC by experts, including HERC's own ad-hoc experts. • ASO agrees with the rating of "Values and Preferences" as "low variability."	Thank you for your comments.
H	2	**1. <u>Following HERC's own published processes requires a finding that the strength of the evidence is "medium" or "high" for ABA for children ages 2 -12</u>** The Draft characterizes the quality of the evidence supporting ABA interventions for young children as "low." However, this determination contradicts HERC's published process.	EbGS believes there is a misunderstanding about the quality of an evidence source and the quality of the evidence on a particular topic. See comment #I1 for reference.

Ident.	#	Comment	Disposition
		Much of the evidence summarized in the Draft qualifies as "high" and "medium" quality evidence. HERC's Biennial Report, presented as an official statement of HERC's process, states: "high quality sources are systematic reviews of prospective cohort studies and evidence-based guidelines from trusted sources, and "medium" quality evidence sources include guidelines issued by professional societies and advocacy organizations, coverage decisions by private health plans, and well-conducted, peer-reviewed individual studies (experimental or observational). "High" quality evidence submitted includes Maglione, a systematic review of prospective cohort studies, which recommends coverage for ABA. Other examples of "high" or "medium" quality evidence under HERC's criteria include: 1. Voluntary coverage of ABA therapy in Oregon by Kaiser Permanente, 2. Several federal district and appellate courts have ordered coverage of ABA therapy, 3. Peer reviewed studies submitted by members of the public demonstrating the usefulness of ABA, and 4. Numerous professional societies and advocacy organizations have endorsed the use of ABA therapy for autism, including: **United States Surgeon General** (see attachment at page 164), **American Academy of Pediatrics**, **Autism Society of America** (our parent group), and **Autism Speaks.** Despite the abundance of "high" and "medium" quality evidence submitted, HERC characterized the evidence as "low" due to the relatively few randomized controlled trials. Nothing in HERC's stated process permits HERC to assess the strength of evidence based on the number of randomized controlled trials or the size of studies. Other evidence was presented to HERC through extensive written and verbal testimony from ad hoc experts and other witnesses. However, no mention of that evidence is made in the Draft.	Citation not provided for Maglione. If referring to the guideline published in Pediatrics, see comment #I6. If referring to the citation in the evidence evaluation, Maglione 2012 is a surveillance report for the AHRQ Warren report. It was a systematic literature search, but not a systematic review (studies were identified, but not analyzed or synthesized), and makes no coverage recommendations. Legal decisions are not evidence sources. HERC is not qualified, nor have they been asked, to come to a conclusion about the merits of case law that may or may not pertain to OHP coverage. The US Surgeon General report is dated 1999 and cites only two studies supporting ABA. Individual studies may be high quality depending on how the study is conducted, but rarely does a single study represent high quality evidence, and commenter does not state which study they believe would qualify. With regard to medium quality evidence, the Biennial report states that they may be examined by the HERC. This does not mean they will be incorporated into guidance, especially if they conflict with a higher level of evidence. Regardless of the quality of the evidence source, the findings concerning the treatment being evaluated are unrelated. For example, the Warren report is a high quality systematic review of the evidence from a trusted source, which finds that there is low quality evidence of effectiveness for ABA in children 2-12, and insufficient

Ident.	#	Comment	Disposition
			evidence for children of other ages. It is the assessment of the Warren report that gave the evidence rating "low", and EbGS did not find additional evidence compelling enough to result in a deviation from this assessment. The coverage guidance process, on which this evaluation of evidence is based, incorporates revisions based on public comment and submitted evidence. Revisions occur once the 30-day comment period ends. The evidence you reference is addressed in this document and the accompanying evidence table.
H	3	**2. Consideration of the evidence presented and HERC's own processes requires a recommendation of coverage for ABA for patients over age 12** The Draft mischaracterizes the evidence of the effectiveness of ABA for patients over age 12 as only one poorly designed case study, and disregarded the evidence presented by Drs. Hagopian, Green, and Riechow at the September meeting. When evidence from these experts is considered, there is sufficient evidence of the effectiveness of ABA to recommend coverage for patients over age 12.	Green provided citations for 2 guidelines and 17 review papers (see evidence table). Citations provided by Hagopian are included in the evidence table. Citations from Reichow include a 2012 Cochrane review of EIBI in children under age 6 with ASD. It included 1 RCT and 4 CCTs, all included in the Warren report, all using treatment as usual as the comparator. Youngest age at entry was 30 months. The review found evidence that EIBI is effective for some children. Authors graded the quality of the evidence as low, with a high risk of bias.
H	4	However, even if the evidence were not sufficient, the Guidance Development Framework approved by HERC requires a recommendation of coverage because denying ABA to patients results in serious disability. The testimony and video from the parents of the young woman who required around-the-clock 2:1 care due to her self-injuring behavior showed clearly that she experienced a serious disability and that focused ABA therapy relieved this behavior. Dr. Hagopian also testified about the use of ABA in older patients to resolve seriously disabling behaviors. Had HERC considered this evidence and applied it to the Framework, it would have lead to a recommendation of coverage for older patients.	The Guidance Development Framework does not "require" any particular decision. It serves only as a general guide, and is accompanied by the following description of its intended use when initially approved in January 2013: "This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general

Ident.	#	Comment	Disposition
			guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following: • Estimate of the level of risk associated with the treatment, or any alternatives; • Which alternatives the treatment should most appropriately be compared to; • Whether there is a discrete and clear diagnosis; • The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives; • The relative balance of benefit compared to harm; • The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests; • Specific indications and contraindications that may determine appropriateness; • Expected values and preferences of patients." This language has been added to the evidence evaluation document for clarity. The Decision Framework is intended to address the evidence supporting a treatment. On the decision framework, the evidence pertaining to ABA in individuals older than 12 is insufficient, treatment risk compared to no treatment is similar or less, treatment is prevalent, and a clinical research study is reasonable (as we have many examples in the literature).

Ident.	#	Comment	Disposition
			Expert opinion and personal testimony are not evidence, Expert testimony serves to provide clinical context for decision-making and may guide decision-making where evidence is mixed or insufficient. Patient testimony is considered as a part of patient values and preferences in the GRADE methodology.
H	5	3. ASO's members are strongly in favor of ABA therapy. The rating of "Values and Preferences" as "low variability" is consistent with the evidence of parents' strong preference for ABA therapy. Parents in Oregon have fought hard for ABA coverage for many years in the legislature and the courts. Families with commercial insurance have pursued and won, and are currently pursuing, federal court cases to obtain ABA. Other families obtained ABA therapy through administrative appeals after denials by their insurance companies. Still other families persuaded their self-insured employers, such as Intel, to voluntarily cover ABA therapy. I am personally aware of the strong preference for ABA therapy among families. My two sons are autistic and enrolled in OHP Plus. Since ABA is not currently covered, we have paid thousands of dollars out of pocket for ABA therapy for our more significantly impacted son. We spent hours training with his therapists, had therapists in our home 25 hours per week year-round, and worked extensively with him during non-therapy hours. We did this because ABA is effective for him in increasing his independence and communication, and in reducing the symptoms of autism. To pay for ABA we sold our home and depleted our savings and retirement funds. However, we had to choose which of our children received ABA because we didn't have the resources to provide ABA therapy to both. Many families also desperately want ABA therapy for their children but can not afford it. The initial determination of "moderate variability" interest was surprising and upsetting as it was admittedly made without any evidence and only by completely ignoring the long-standing fight by parents to get ABA therapy for their children. We agree with the change to "low variability." **References:** 1. Prioritization of Health Services: A Report to the Governor and 77th Oregon Legislative Assembly (2013) 2. Mental Health: A Report of the Surgeon General (1999). Attached are the Title Page through Table of Contents and pages 151-174. See page 165.	Thank you for your comment.
I	1	Public Comment: HERC's 2013-2015 biennial "PRIORITIZATION OF HEALTH SERVICES: A Report to the Governor and the 77th Oregon Legislative Assembly" provides the following definition of "High Quality" evidence	Thank you for providing this reference. This document further states: "Clinical judgment will still need to be used by the Commission to determine whether the

Ident.	#	Comment	Disposition
		(Chapter 1, page 21): "The following types of evidence are considered *high quality*: • Systematic reviews of randomized controlled trials • Systematic reviews of prospective cohort studies • Evidence-based guidelines from trusted sources"	available evidence is sufficient and compelling enough to affect prioritization decisions." A high quality source may still result in low quality evidence. It means the methodology used to review evidence involved a rigorous approach, but the underlying evidence was still of low quality. See comment #H3.
I	2	Evidence-based guidelines from sources from trusted sources: Warren, *Comparative Effectiveness Review # 26: Therapies for Children With Autism Spectrum Disorders*, AHRQ Age Range reviewed: 2 to 12 *Key findings:* • "Evidence supports early intensive behavioral and developmental intervention, including the University of California, Los Angeles (UCLA)/Lovaas model and Early Start Denver Model (ESDM) for improving cognitive performance, language skills, and adaptive behavior in some groups of children." (p. vi) • "Within this category, studies of UCLA/Lovaas-based interventions report greater improvements in cognitive performance, language skills, and adaptive behavior skills than broadly defined eclectic treatments available in the community. However, strength of evidence is currently low." (page ES-7)	Warren is a systematic review, not a guideline. However, this report does serve as the evidence base for recommending coverage for children ages 2 to 12, and assesses the strength of the evidence for ABA to be low. EbGS agrees with the findings for ages 2-12 and agrees the strength of evidence is low.
I	3	New Zealand Guidelines Group, Guideline Supplementary Paper -- New Zealand Autism Spectrum Disorder Guideline Supplementary Evidence on Applied Behaviour Analysis Age Range reviewed: 0 to 14 *Key Findings:* • "Interventions and strategies based on applied behaviour analysis (ABA) principles should be considered for all children with ASD." (Grade A) [The recommendation is supported by GOOD evidence (where there is a number of studies that are valid, applicable and clinically relevant)] • "Early intensive behavioural intervention (EIBI) should be considered as a treatment of value for young children with ASD to improve outcomes such as cognitive ability, language skills, and adaptive behaviour." (Grade B) [The recommendation is supported by FAIR evidence (based on studies that are mostly valid, but there are some concerns about the volume, consistency, applicability and/or clinical relevance of the evidence that may cause some uncertainty, but are not likely to be overturned by other evidence).]	Thank you for providing this reference. This guideline, initially published in 2008 and updated in 2010, was rated fair quality in the WA HTA report. NZ guideline also states, "There is a lack of knowledge about the suitability of ABA for persons with an Asperger Syndrome diagnosis, and for participants aged 15 years or above" For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.

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I	4	Systematic Reviews of randomized controlled trials and prospective cohort studies: IMPAQ International, LLC, *Final Report on Environmental Scan, Autism Spectrum Disorders (ASDs) Services Project*, for Center for Medicaid and Medicare Services Age Range reviewed: 0 to 21 (children and transitioning youth) *Key Findings:* • Identified 15 ABA, Developmental, and other behavioral interventions as "Established" for children • Identified 1 ABA (antecedent) intervention as "Established" for transitioning youth	This report grouped interventions into 3 categories: evidence-based, emerging or unestablished. The one intervention considered established for transitioning youth (ages 17-21) was the antecedent package (interventions that "focus on modifying the conditions or events that usually precede the occurrence of targeted behavior(s), with the objective of increasing the success of a preferred behavior"). The authors state that their assessment was based on review of 2 studies, but only one citation is provided, which was for an interrupted time series study with a sample size of 3.
I	5	Clinical Practice Guideline Report of the Guideline Recommendations Autism / Pervasive Developmental Disorders Assessment and Intervention for Young Children (Age 0-3 Years), New York State Department of Health Early Intervention Program Age Range: 0 to 3 *Key Findings:* • "It is recommended that principles of applied behavior analysis (ABA) and behavior intervention strategies be included as an important element of any intervention program for young children with autism. [A]" • "It is recommended that intensive behavioral programs include as a minimum approximately 20 hours per week of individualized behavioral intervention using applied behavioral analysis techniques (not including time spent by parents). [A]"	This guideline was sponsored by NY DOH, but was created by a panel of parents and professionals. It is not dated, but appears to have been created in 2005. It states that it is not intended to be a policy document or a required standard of practice for NY DOH. 19 articles cited as SSRD are listed as evidence, as well as other studies that were included in Warren 2011 which did not include children <2. Full text of guideline not available without purchase.
I	6	Maglione, M.A. et al, "Nonmedical Interventions for Children With ASD: Recommended Guidelines and Further Research Needs," *Pediatrics*, 2012 Age Range: 3 to 17 *Key Findings:* • Developed consensus guidelines on nonmedical interventions that address cognitive function and core deficits in children with autism • Guidelines were developed by a Technical Expert Panel (TEP) based on a systematic overview of research findings • "The TEP agreed that children with ASD should have access to at least 25 hours per week of comprehensive intervention to address social communication, language, play skills, and maladaptive behavior. They agreed that applied behavioral analysis … have shown efficacy." • Strength of Evidence for ABA was "Moderate"	AHRQ and GRADE methodology utilized. Excluded SSRD studies. Authors state the following: "In addition, the criteria for including a study in our review were more rigorous than in previous reviews that included single subject research designs. Such reviews have been used to create "evidence-based" standards that in fact do not reflect accepted principles of evidence-based practice. Still, our own guideline statements are based largely on expert opinion, with the systematic review as a starting point."

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			With regard to individuals older than 12, the guideline states: "The comprehensive interventions we identified were targeted mainly to young children. These types of behavioral interventions, parent training programs, environmental support, and developmental interventions rarely studied adolescents and thus provided limited information on the characteristics of effective programs for adolescents or adults." The SR supporting the guideline does not include specific ages, but only refers to age as child or adolescent. Authors were able to evaluate the effect of age only for social skills interventions, and age was not identified for any of the other interventions. Of the studies of social skills interventions, 3 included both children and adolescents, 4 included children only and 3 included adolescents only. Of those that included only adolescents, there was statistically significant benefit found in 1 of the 3 included studies. While the results of the other 2 did not reach statistical significance, pooling the 3 studies did result in a statistically significant result. Evidence was not reported separately by age for any other type of intervention. *For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.*
I	7	Guidelines issued by government agencies: Numerous state and federal government agencies have issued evidence-based guidelines on ABA. While they are not on HERC's list of "trusted sources," they should be given stronger weight than "Guidelines issued by professional societies and advocacy organizations" which meet HERC's	These key findings do not appear to conflict with the current recommendations in the evidence evaluation.

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		definition of "Medium Quality" evidence. This is a review of one particularly relevant recommendation from the Interagency Autism Coordinating Committee, signed by the Director of the National Institute for Mental Health, on coverage of ABA in Medicaid. Letter from Interagency Autism Coordinating Committee to DSHS Secretary Sebelius Age Range reviewed: Not specified *Key Findings:* • "While intensive behavioral interventions are expensive, they are effective and recent data support that they are cost-effective, mitigating these long-term costs of disability. Research tells us that treatment works. As a result, the American Academy of Pediatrics and the United States Surgeon General have endorsed these interventions." • "A Federal minimum standard of autism coverage should be set for all health plans offered in the individual and small group markets. Minimum coverage should include evidence-based early intervention—including but not limited to ABA—for children with ASD, at a level of intensity indicated by the evidence."	
J	1	HERC's 2013-2015 biennial "PRIORITIZATION OF HEALTH SERVICES: A Report to the Governor and the 77th Oregon Legislative Assembly" provides the following definition of "Medium Quality" evidence (Chapter 1, page 22): "The following sources are considered medium quality and are often examined by the HERC. * Guidelines issued by professional societies and advocacy organizations (e.g. American Heart Association) * Coverage decisions by private health plans (e.g. Aetna) * Well-conducted, peer-reviewed individual studies (experimental or observational)" The CD-ROM submitted contained numerous pieces of evidence that meet this definition of "Medium Quality" evidence. This comment focuses on coverage decisions made for health plans – including private plans, government-administered health plans, and Medicaid programs in other states – by courts of law, which have consistently found that ABA therapy is evidence-based and that decisions to exclude it were arbitrary, capricious, and contrary to law. Medicaid:	The HERC may examine these additional sources, but generally will not make recommendations based on them, especially if they conflict with higher quality evidence. See comment #H3.
J	2	We have described two specific court orders from Florida and Ohio. The CD-ROM also contains Medicaid opinions and settlement agreements from Louisiana, Michigan, and Washington. **Florida – Garrido v Dudek** Age Range: 0 to 21	Legal decisions are not considered evidence; they are the result of a legal process, and have been known to mandate coverage for treatments later shown to be ineffective or harmful (e.g., bone marrow transplant in

Ident.	#	Comment	Disposition
		Key findings: * "17. ABA is "medically necessary" and is not "experimental" as defined under Florida administrative law and federal law." * "19. ABA is indisputably considered by the medical community to be the standard means of treatment for children with ASD." * "20. ABA is indisputably considered proven and effective by the medical community." * "21. There is a plethora of medical and scientific literature including peer-reviewed meta-analyses, studies, and articles conclusively showing that ABA is a proven and effective treatment to prevent disability and restore developmental skills to children with autism and ASD." * "25. It is unreasonable to solely consider large-scale randomized controlled trials when evaluating ABA's efficacy because these trials are not appropriate or feasible for the vast majority of ABA research involving children with ASD, and it is unethical to have a control group, i.e., a group of children not getting ABA therapy." * "28. The Defendant violated EPSDT provisions of the Medicaid Act by excluding coverage of Applied Behavior Analysis (ABA) for Medicaid-eligible recipients under 21…." **Ohio – PLEASE v Jones Kelley** Age Range: 0 to 21 Key findings: * "ABA therapy, when recommended by a licensed practitioner of the healing arts, is a medically necessary service which provides the maximum reduction of a mental or physical disability." * "For an autistic child, 'the best treatment plan will include ABA [applied behavioral analysis], the only treatment approach confirmed as effective by a comprehensive evaluation of all proposed therapies in a well known government sponsored review process.'" * "ABA therapy is 'a highly effective form of behavioral treatment in virtually all cases'" * "If the Plaintiff children are no longer able to receive the medically recommended 35-40 hours of ABA therapy per week, there is sufficient evidence that the children will experience regression."	breast cancer) and are related to the facts or contexts of a particular case.
J	3	**Private and Government Employer Health Plans:** **PacificSource – McHenry v PacificSource** Key Findings: * "ABA therapy is firmly supported by decades of research and application and is a well-established treatment modality of autism and other PDDs. It is not an experimental or investigational procedure" (document 59, 1/5/10, page 19) **Tricare – Berge v United States of America**	See comment #J2.

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		Key Findings: * "… the assessments cited by the Agency suggest that behavioral modification therapy is the closest intervention medical professionals have identified as the standard means for treating autism. … (ABA is "the dominant and preferred treatment modality" for autism). Therefore, this Court is left to wonder what forms of autism treatment would satisfy the Agency's regulatory requirement of being proven when the very sources the Agency relies upon to declare ABA therapy unproven cannot identify one form of treatment that is more effective than ABA therapy. Since the Agency has failed to articulate a reasoned explanation for its determination that ABA therapy is unproven, particularly in light of evidence before it suggesting the contrary, the Court must conclude that the Agency's determination is arbitrary and capricious." * "Agency's denial of ABA therapy coverage under the Basic Program is arbitrary and capricious" **Blue Cross Blue Shield – Potter, Boyer v Blue Cross Blue Shield of Michigan** Key Findings: * "Given that the studies in the record almost uniformly conclude that ABA is effective, and make almost no distinction between types of autism spectrum disorder, the Court finds that the 2010 medical policy's statement that ABA's effectiveness 'in the treatment of certain types of autism spectrum disorders has not been established' is not supported by the record." * "The medical policy also does not describe why 'several studies' providing relatively long follow-up data does not constitute 'enough long-term studies.' To the extent BCBS relies on the numerical insufficiency of the long-term studies of ABA therapy, its policy is internally inconsistent and unsupported; reliance on it to determine benefits would be arbitrary and capricious." * "… with respect to randomization, the studies cited in the medical policy state that randomized studies of ABA therapy are unavailable for ethical and practical reasons, and the single randomized study cited in the policy confirmed ABA's efficacy." * "It is further ordered that Defendant's characterization and exclusion of ABA therapy as experimental or investigative, as applied to the claims of the class members, was, and is, arbitrary and capricious."	
K	1	HERC's 2013-2015 biennial "PRIORITIZATION OF HEALTH SERVICES: A Report to the Governor and the 77th Oregon Legislative Assembly" provides the following definition of "Medium Quality" evidence (Chapter 1, page 22). "The following services are considered medium quality and are often examined by the HERC: Guidelines issued by professional societies and advocacy organizations (e.g., American Heart Association) Coverage decisions by private health plans (e.g., Aetna)	The HERC may examine these additional sources, but generally will not make recommendations based on them, especially if they conflict with higher quality evidence. SSRD studies were included in the source reports when

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		Well-conducted, peer-reviewed individual studies (experimental or observational)" The CD-Rom submitted contained numerous pieces of evidence that meet this definition of "Medium Quality" evidence. This comment reviews several guidelines for coverage of ABA issued by professional and advocacy organizations. **Guidelines issued by professional societies and advocacy organizations:** American Academy of Child and Adolescent Psychiatry Key findings: "Early and sustained intervention appears to b particularly important, regardless of the particular philosophy of the program, so long as a high degree of structure is provided. Such programs have typically incorporated behavior modification procedures and applied behavior analysis. These methods build on a large body of research on the application of learning principles to the education of children with autism and related conditions. Procedures that strengthen desired behaviors and/or decrease undesired maladaptive behaviors are utilized in the context of a careful and individualized plan of intervention based on observation of the individual. It is clear that behavioral intervention can significantly facilitate acquisition of language, social, and other skills, and that behavioral improvement is helpful in reducing levels of parental stress." **National Autism Center:** Key findings: Developed by an expert panel: "based on a thorough review of the educational and behavioral treatment literature that targets core characteristics and associated symptoms of ASD that was published between 1957 and the fall of 2007" Identified "11 Established Treatments: treatments that produce beneficial outcomes and are known to be effective for individuals on the autism spectrum. The overwhelming majority of these interventions were developed in the behavioral literature (e.g., applied behavior analysis, behavioral psychology, and positive behavior support)." **American Academy of Pediatrics** Key findings: "The effectiveness of ABA-based intervention in ASDs has been well documented through 5 decades of research by using single-subject methodology and in controlled studies of comprehensive early behavioral intervention programs in university and community settings. Children who receive early intensive behavioral treatment have been shown to make substantive, sustained gains in IQ, language, academic performance, and adaptive behavior as well as some	they met specific inclusion criteria. These findings do not appear to conflict with the current recommendations in the evidence evaluation.

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		measures of social behavior, and their outcome have been significantly better than those of children in control groups."	

L	1	This summarizes my feedback on the draft report on ABA as a treatment for autism. In general:
		• I support the strong recommendation in favor of ABA coverage for younger children
		  ○ The quality of evidence is – by HERC standards – Medium or High, not low
		  ○ There should be no minimum age for ABA – children under 2 should be given access to ABA upon diagnosis
		• Patients over the age of 12 should be given coverage for ABA when medically necessary
		  ○ There is sufficient evidence to support the effectiveness of ABA for older patients
		  ○ For some patients with severe symptoms, such as self-injurious behaviors, a failure to treat can result in severe disability. By HERC's process, this requires a "strong" recommendation in favor of coverage even if evidence is insufficient.
			See comments #G1, #H2 and #H3.

L	2	<u>Background – Page 1:</u> The first paragraph includes the sentence "The bill also directs insurers to cover ABA therapy up to a maximum of 25 hours per week for children who initially seek care before age nine, and allows continued coverage until age 18." This isn't an accurate description of SB365. It should be replaced with the following: "The new law also establishes requirements for state-regulated health plans to approve and manage autism treatment, including ABA and any other medical or mental health services identified in an individualized treatment plan. The law applies to patients who begin treatment before age 9, covering up to 25 hours of ABA per week, and continuing for as long as medically necessary regardless of age. Existing Oregon laws requiring coverage of autism treatment (ORS 743A.168 and 743A.190) continue to apply to older patients and those seeking more than 25 hours of ABA per week." This section should also include the definition of Applied Behavior Analysis from SB365 Section 2(1).	Evidence evaluation background section changed to reflect this verbiage, definition of ABA added. ORS743A.190 and ORS743A.168 do not apply to Medicaid.
L	3	<u>Evidence Sources and Summary of Evidence – pages 2 to 15:</u> All of the sources listed are Comparative Effectiveness Research. As required by ORS 414.701, it must be expanded to include other sources. Please refer to the CD-ROM I submitted, and the attached list of references, for other High and Medium Quality sources.	See evidence table. Total of 336 unduplicated citations provided by all commenters. Detailed review limited to experimental designs that included individuals over age 12. Random sample of SSRD studies reviewed, as well as all SR or MA of SSRD studies.

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			EbGS utilizes the GRADE methodology for making recommendations, which includes incorporation of values and preferences. The EbGS also considered testimony from three appointed experts on ABA, and is considering additional public testimony during this 30 day public comment period. In addition, the material relied upon in the evaluation of evidence is not solely or even substantially comparative effectiveness research. The Warren report, while referred to as a comparative effectiveness review, also included at least 11 case series or chart reviews, and the additional information from the Maglione report included 4 case series. Many of the cohort studies and controlled trials compared ABA to waitlist, not another intervention. See comment #X2
L	4	<u>GRADE Informed Framework – page 16:</u> *ABA for adolescents and adults*: We have provided additional evidence and testimony, including sources that meet HERC's definition of "Medium" and "High" quality, to support coverage for patients over the age of 12. The "insufficient" quality of evidence rating should be upgraded to Medium or High. *Quality of Evidence:* There is a footnote reading: "The Quality of Evidence rating was assigned by the primary evidence source. The HERC has made its own assessment of the quality of the evidence after the review of the studies contained within the AHRQ surveillance report." This is inconsistent with the definition of High, Medium and Low quality evidence that we were provided by HERC's attorney, as documented in HERC's 2013-2015 report to the Governor and Legislature, Chapter 1: "The following types of evidence are considered high quality: • Systematic reviews of randomized controlled trials	See comment #H2. HERC does not have a specifically appointed attorney. The material provided to this commenter was from the OHA communications office. Although there appears to be a misunderstanding about the quality of an evidence source and the quality of evidence that supports (or does not support) an intervention, the Warren report pertains only to children ages 2 to 12, not adolescents and adults as suggested in this comment.

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		• Systematic reviews of prospective cohort studies • Evidence-based guidelines from trusted sources" … The following sources are considered medium quality and are often examined by the HERC. • Guidelines issued by professional societies and advocacy organizations (e.g. American Heart Association) • Coverage decisions by private health plans (e.g. Aetna) • Well-conducted, peer-reviewed individual studies (experimental or observational); there is ample Medium and High quality evidence for all Indications listed." By HERC's definition, an Evidence-based guideline from a trusted source – such as AHRQ CER26 by Warren (2011) or Maglioni (2012) is by definition "High Quality" evidence. Since there is High Quality evidence supporting ABA as effective, the "Quality of Evidence" should be rated "High" rather than "Low."	
L	5	<u>Summary Conclusions – page 17:</u> *For patients ages 2-12:* There is no evidence that ABA would be ineffective or harmful for patients under the age of 2. There should be no minimum age for treatment – patients should be provided coverage for ABA therapy upon diagnosis.	The Warren report only addressed children from 2 to 12. While it is correct that there is no evidence that ABA is ineffective or harmful, stewardship of scarce resources guides the HERC work of limiting coverage to those treatments that have evidence of effectiveness. According to one of the appointed experts, "The age at which treatment should be started is also uncertain. … We do not have strong evidence that starting a treatment at 24 months, as opposed to 36 months, will produce more gains, and if yes which ones." In response to expert opinion, EbGS lowered the recommended age to consider treatment to one year.
L	6	As discussed in the 11/7/2013 EbGS meeting, the GRADE framework on page 16 references "EIBI for children aged 2 to 12 years at initiation" – indicating that the recommendation was for patients who start ABA by age 12 but could then continue beyond that age. This should be reflected in the Summary Conclusion.	*EbGS recommends coverage of EIBI for patients up to age 12; for older patients EbGS recommends 8 hours per month of ABA.*
L	7	*Parent / Caregiver involvement:*	The summary conclusions state that parent/caregiver

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		I support parent involvement and training. However, the SB365 definition of ABA is based on professionally administered therapy. All patients should have access to professionally administered treatment; no patient should be denied coverage if parents are unable to participate.	involvement is recommended; it does not say required. Expert testimony reinforced the importance of parent involvement, and some studies included in the evidence evaluation addressed parent-administered therapy.
L	8	*For patients over the age of 12:* While there has been more research into ABA for younger children, HERC's report has not documented any research showing "that ABA is most effective when administered at younger ages….." There is ample Medium and High quality evidence for the effectiveness of ABA with patients over the age of 12, as documented in the CD-ROM and attached reference list. Even if HERC were to conclude that evidence was "insufficient," a failure to treat ABA in older patients can cause very severe disability, making a clinical trial unreasonable per HERC's criteria. Therefore, HERC process calls for a strong recommendation in favor of coverage for older patients.	The quoted statement has been deleted from the summary conclusions. See evidence table with regard to CD-ROM. See comment # H4 regarding the HERC decision framework.
L	9	<u>Appendix B – Potentially Applicable Codes – page 21:</u> In addition to the codes you have listed, HERC should consider the following: • Kaiser uses codes G0176 and G0177 • Many insurers use codes 90806 and 90808	Thank you for these suggestions. Specific coding is beyond the scope of this guidance, but this information may be useful to others. Codes added. • G0176 – Activity therapy, such as music, dance, art or play not for recreation, related to the care and treatment of patient's disabling mental health problems (45 min or more) • G0177 – Training and educational services related to the care and treatment of patient's disabling mental health problems (45 min or more) • 90806 – discontinued code; bill 90834 – psychotherapy, 45 min • 90808 – discontinued code, bill 90837 – psychotherapy, 60 min
L	10	<u>Appendix C – HERC Guidance Development Framework – pages 22 and 23:</u> For the assessment on page 23 for older patients, we disagree: • Level of Evidence should be considered Sufficient. This would then follow the same path as	The Guidance Development Framework is not directive, but serves only as a framework for consideration; see comment #H3.

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		for younger patients on page 12, with a "Strong Recommend" result. • Even if HERC concludes that evidence is Insufficient, a clinical research study is not reasonable, since failure to perform ABA for some severely impacted patients is likely to result in serious disability or even death, in the case of self-injurious behavior. This also produces a "Strong Recommend" result.	If there is insufficient evidence to support an intervention, even if the underlying disease is very severe, it is unknown whether or not that intervention would be helpful, and thus does not compel support. The example of bone marrow transplant for breast cancer is illustrative.
M	1	My understanding is that the committee has decided to accept the evidence for treatment of children up to the age of 12 as sufficient to make a recommendation, and as I have previously submitted sufficient supporting evidence for that recommendation, I will focus in these comments on the evidence for treatment of older children.	Thank you for your comment.
M	2	**Regarding publication bias.** This consideration has to be considered a moot point, because all peer-reviewed evidence of any kind is subject to the same risks. This is why the AAP (2013), the SAMHSA (2007), and others recommend that considerations of evidence be based also upon published expert reviews, which can take into account the relative risks and plausibility of findings. On the issue of the exclusive reliance upon RCTs, these are emphatically not the sole form of science, and in actuality, the field of ABA was developed in reaction to their shortcomings. The real knowledge of science comes from laboratory research where we directly manipulate the biological process and observe the results – in the single organism. In the case of ABA, a publication of this form of evidence will include both the failures and the successes, because due to its laboratory nature, the study directly compares a failed treatment with a successful form of treatment in the same child. The technical manipulation of parameters, with replications of the effect across repeated measures, makes it entirely unlikely that some kind of spurious conclusion is being published. This model of experimentally controlled research within single subjects is also best suited to advance our understanding of autism, because the presenting problems are so heterogeneous. It is daunting to compile a large group of participants and compare them with matched controls, when the dependent measures are of such widely varying types. The heterogeneity is the focus of the large scale studies of older children's treatment. Approximately half of the studies are "functional analyses." These are studies which explicitly compare several possible treatments to weed out the ineffective from the effective treatments. Such purposeful experimental manipulations and reports of failures and successes lessen the likelihood of publication bias.	See evidence table. Publication bias occurs when "negative" studies are not published. While it is true that all evidence may be subject to publication bias, statistical tests can be done to assess the degree to which that exists in clinical research. EbGS is unaware of statistical tools to assess this in SSRD. The primary sources for this evidence evaluation do not rely exclusively on RCTs, and include observational studies as well as SSRD when those studies meet specific criteria.

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M	3	**What is the evidence for treatment of older age children?** In the research listed here, over 2,000 children and adolescents who were between the ages of five and twenty-one were documented as receiving effective ABA treatment.	See evidence table. Of the citations provided, 102 included individuals over 12, while for 111, age was not specified in the abstract, or was not applicable.
M	4	Reichow and Volkmar, in 2010, reported on 31 studies of children, aged four to fifteen, who benefited from ABA social skills training: "The school-age category had the highest participant total of the three age categories (N = 291)."(page 156). "Within the last 8 years, 66 studies with strong or acceptable methodological rigor have been conducted and published. These studies have been conducted using over 500 participants, and have evaluated interventions with different delivery agents, methods, target skills, and settings. Collectively, the results of this synthesis show there is much supporting evidence for the treatment of social deficits in autism." (page 161).	The authors of this systematic review go on to state the following: "No interventions for preschool aged children or adolescents and/or adults had enough support to be considered … EBP [evidence based practice] based on the results of this review. Social skills groups for school-aged children with ASD demonstrated the evidence necessary to be considered an established EBP." And "the EBP criteria were not applied to three of the most commonly used intervention categories (i.e., ABA, parent training, peer training) due to the variability in intervention procedures within the techniques classified." For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
M	5	Bellini and colleagues, in 2007, reported the following age ranges of 155 children who benefited from ABA social skills training: "21 studies involved preschool-age children, 23 involved elementary age children, and 5 studies involved secondary-age students." (page 158).	This is a meta-analysis of school-based social skills interventions. ABA is not mentioned, and it is not clear which interventions the commenter considers ABA.
M	6	Brosnan and Healy, in 2011, reported on 18 studies of children aged three to 18, who received effective ABA treatment to reduce or eliminate severe aggressive behavior: "All of the studies reported decreases in challenging behavior attributed to the intervention. Of the studies included, seven reported total or near elimination of aggression of at least one individual during intervention in at least one condition." (page 443). "only four of the studies conducted follow-up assessments. However, each of these studies reported that treatment gains were maintained." (page 443).	Of the 18 included SSRD studies, 5 included children over 12. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.

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M	7	Lang, et al. in 2010, reported on nine studies which involved 110 children aged nine to 23, who received a variety of forms of behavior therapy for anxiety. "Within each reviewed study, at least one dependent variable suggested a reduction in anxiety following implementation of CBT." (page 60). "CBT has been modified for individuals with ASD by adding intervention components typically associated with applied behaviour analysis (e.g. systematic prompting and differential reinforcement). Future research involving a component analysis could potentially elucidate the mechanisms by which CBT reduces anxiety in individuals with ASD, ultimately leading to more efficient or effective interventions." (page 53).	SR limited to treatment of anxiety (not core symptoms of autism) using modified CBT. Study details not available regarding age, other than range. Treatment of associated symptoms (anxiety) is beyond the scope of this evidence evaluation.
M	8	Hanley, Iwata, and McCord in 2003, reported on 277 studies which involved 536 children and adults (70% of the studies included persons between the ages of 1 and 18, and 37% also included persons older than 18), who received functional analyses of problem behaviors. Of these, 96 percent were able to yield an analysis of the controlling variables of the problem behavior. The specific functional analysis of individual problem behaviors is crucial to the successful intervention with those behaviors. "Large proportions of differentiated functional analyses showed behavioral maintenance through social-negative (34.2%) and social-positive reinforcement (35.4%). More specifically, 25.3% showed maintenance via attention and 10.1% via access to tangible items. Automatic reinforcement was implicated in 15.8% of cases." (pages 166-167).	Only 58 of the 277 SSRD studies included individuals with autism. 70% of studies included children, defined as < 18. No other information on age provided. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
M	9	Iwata and colleagues, in 1994, reported on the effective treatment of self-injurious behavior with 152 children, adolescents, and adults. In their sample, 39 were between the ages of 11 and 20, and 74 were 21 and older. The function of the self-injurious behavior could be identified in 95% of the persons, and in 100% of those cases an effective treatment could then be prescribed. "Across all categories of intervention, restraint fading was the most effective, but its 100% success rate is misleading because it was always implemented in conjunction with another procedure. As single interventions, EXT (escape) had the highest success rate (93.5%); sensory integration and naltrexone had the lowest (0%)." (page 233). "Results of the present study, in which single-subject designs were used to examine the functional properties of SIB in 152 individuals, indicated that social reinforcement was a determinant of SIB in over two thirds of the sample, whereas nonsocial (automatic) consequences seemed to account for about one fourth of the cases." (page 234).	The number of individuals with autism, if any, is not specified. (population included patients with mental retardation)
N	1	Please accept these public comments in favor of requiring OHP coverage for applied behavior analytic (ABA) services for individuals of ALL AGES with autism spectrum disorders (ASD). After reading the draft evaluation of evidence, I am left concern that the committee tasked with evaluating existing science in this area did not have adequate representation from someone with expertise in behavior analysis and single subject design (SSD) research. ABA is the applied arm of	Thank you for this explanation. SSRD studies were included in the evidence source if they met criteria.

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		behavior analysis, which is a science of human behavior. Behavior analysis seeks to best understand the principles that elicit and evoke behavior at the individual level. Thus, by definition, behavior analysis (and its applied arm ABA) are idiographic in nature. As a result, the primary method for studying behavior is at the individual level and involves use of SSD. Such an approach has much greater internal validity than group design research and is particularly relevant to intervention research since, for the most part, intervention is delivered at the individual level.	
N	2	Unfortunately, certain assumptions regarding which research would be included in the HERC review lead to exclusion of the vast majority of research on the application of behavior analytic principles for addressing different behavioral targets displayed by individuals with ASD; notably, the requirement that at least 10 subjects be involved in research for a study to be included results in most of the research to be excluded. No justification for this number is provided. Why is 10 better than 9? Why is 10 good enough? Research utilizing single subject design involves control comparison, albeit in a different way than group design. However, I argue that within subject comparison (the hallmark of SSD) is a better comparison that between-group comparison as it emphasizes behavior change at the individual level (again, the target of intervention). With inclusion of research based on SSD, a markedly different understanding of the strength of research on ABA with individuals with ASD is likely to emerge.	The rationale for limiting inclusion criteria in the Warren report to at least 10 participants is reported as follows: "We recognize that setting a minimum of 10 participants for studies to be included effectively excluded much of the literature on behavioral interventions using single-subject designs. Because there is no separate comparison group in these studies they would be considered case reports (if only one child included) or case series (multiple children) under the rubric of the EPC study designs. Case reports and case series can have rigorous evaluation of pre- and post- measures, as well as strong characterization of the study participants, and case series that included at least 10 children were included in the review. **Single-subject design studies can be helpful in assessing response to treatment in very short timeframes and under very tightly controlled circumstances, but they typically do not provide information on longer term or functional outcomes, nor are they ideal for external validity without multiple replications.** They are useful in serving as demonstration projects, yielding initial evidence that an intervention merits further study, and, in the clinical environment, they can be useful in identifying whether a particular approach to treatment is likely to be helpful for a specific child. Our goal was to identify and review the best evidence for assessing the efficacy and effectiveness of therapies for children with ASD, with an eye toward utility in the treatment setting.

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			With the assistance of our technical experts, we selected a minimum sample size of 10 in order to maximize our ability to describe the state of the current literature, while balancing the need to identify studies that could be used to assess treatment effectiveness." See comment #F2 regarding recommended standards for evidence in SSRD.
N	3	What the committee is also encouraged to consider is that ABA is not 1 technique, or even one package of techniques. While there are manualized packages described based on ABA, the vast majority of research on the effects of ABA on ASD do not utilize such an approach. Again, this is because the science of behavior analysis, and thus ABA, is idiographic. Considering ABA as a single intervention, much like one might say Ritalin or Prozac are single interventions, rather than as a broad range of strategies based on the theory and principles of behavior analysis is problematic. It leads to a reductionist view of the definition of an intervention. Rather, a more robust approach to reviewing existing research might be to define common specific interventions and analyze the effects of those interventions on behavioral targets, or to take behavioral targets and analyze the effects of behavioral interventions on those targets. Meta-analytic approaches for use with SSD research are described in the research and could be utilized to better understand the full literature on ABA in ASD. Thus, although I am critical of the approach to the review of the evidence, and I encourage future reviews to include people with expertise in behavioral analysis and SSD, I support the recommendation for inclusion of ABA therapies when those therapies are directed by people with appropriate training and expertise in the field of behavior analysis.	HERC was not provided the resources to conduct a de novo review of the literature as suggested by the commenter. The Warren report utilized a technical expert panel that included "technical experts on the topic of ASDs in the fields of developmental disabilities, psychiatry, psychology, occupational therapy and educational research to provide assistance during the project … including representatives from our partner organizations (the nominators of the topic), the Medicaid Medical Directors and Autism Speaks. To ensure robust, scientifically relevant work, we called on the TEP to provide reactions to work in progress or possibly overlooked areas of research. TEP members participated in conference calls and discussions through e-mail to: • Refine the analytic framework and key questions at the beginning of the project; • **Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;** • Provide input on assessing the quality of the literature. "
N	4	I strongly urge the HERC to reverse its recommendation against support for ABA for individuals above the age of 12. No specific rationale is provided for this as a cut-off age. Why 12? Why not 11? Why not 13? Particularly with people with developmental disabilities, chronological age is likely an ineffective proxy for any meaningful decisions regarding treatment. While the committee's review suggests that	The evidence of effectiveness of ABA is limited to children ages 2-12, based on the Warren report. Rationale for limiting the report to those ages is as follows:

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		there is insufficient evidence for ABA beyond the age of 13, again I submit that the literature review conducted by this committee is overly narrow and limited based on several decisions regarding its review approach.	"we chose to limit the age range to 2–12 because a) diagnosis of ASDs earlier than age 2 is less established and b) adolescents likely have substantially different challenges and would warrant different interventions than children in the preschool, elementary and middle school age groups. We did, however, add one question (KQ7) focusing on children under age 2; children in this age group are not definitively diagnosable, but may be at risk either because they have a sibling with ASDs, or they may be exhibiting signs suggestive of a possible ASD diagnosis." The Lounds 2012 report that addressed individuals over age 12 found insufficient evidence of effectiveness.
N	5	I agree that existing research suggests that certain interventions that are designed to address core symptoms of ASD may have the greatest impact when implemented with young children. However, many people with ASD display a range of problematic behaviors that are not part of core diagnostic features (e.g., self-injury, aggression) that can be effectively treated using techniques based on the principles of behavior analysis. Further, again by including a more robust representation of the literature on the use of behavior analytic interventions for people with ASD of all ages by looking at SSD research, the committee is likely to come to a very different conclusion regarding whether a cut of age of 12 is meaningful in any particular way.	See comment #N2
N	6	In conclusion, I am strongly in support of coverage for applied behavior analytic treatments for individuals OF ALL AGES with ASD, when delivered by professionals with training and expertise in the science and practice of behavior analysis. The committee is strongly encouraged to provide a more appropriate review of the extant literature by including the thousands of studies that utilize SSD. While RCTs have many benefits, they are not internally valid and do nothing to tell us the effects of an intervention at the individual level. At the very least, a balanced review of the literature that appreciates both the strengths and weaknesses of SSD research and RCTs is encouraged. It is very likely that such an approach would result in even stronger recommendations for coverage of ABA for ASD, and for such coverage for individuals of all ages.	EbGS disagrees that RCTs are not internally valid. Internal validity relates to the magnitude of bias, and is defined in the User's Guides to the Medical Literature as: "Whether a study provides valid results depends on whether it was designed and conducted well enough that the study findings accurately represent the direction and magnitude of the underlying true effect." No citations provided. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be

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			considered medically appropriate for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
O	1	As a clinician who has worked for years with people affected by ASD, I applaud the Commission's efforts in favor of ABA inclusion as a prioritized treatment. I would also assert that (1) there should be no minimum age of 2 years for ABA, as younger diagnosed children can benefit substantially from behavioral treatment when clinically indicated and (2) patients over the age of 12 should be given coverage for ABA when indicated, as it is often an important treatment component to address behaviors which can significantly impair older youth's and adult's functioning (e.g. aggression, feeding, etc.)	Thank you for your comment. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
P	1	Autism Speaks appreciates the opportunity to offer comments in response to the draft HERC report regarding Applied Behavior Analysis for Autism Spectrum Disorder. We are pleased that the needs of the autism community are increasingly a priority in Oregon and that the state has taken positive and concrete steps to address this critical health issue, including access to evidence based treatment including Applied Behavior Analysis. Most recently, we worked closely with Oregon legislators, state officials, disability organizations, and families to secure the enactment of autism insurance legislation during the 2013 legislative session. This legislation—and the work of the Oregon Health Evidence Review Commission—is vital for services needed by an estimated 1 in 88 individuals diagnosed with an autism spectrum disorder.	Thank you for your comment
P	2	Autism Speaks supports meaningful access to coverage based on medical necessity and recognizes that medical needs can vary *significantly* for each individual diagnosed with autism. Treatment decisions—including the nature, intensity, and duration of services—should be made by the treatment team and individualized to the needs of each family. Specifically, recommending that Applied Behavior Analysis only be provided through the arbitrary age of twelve is problematic. Please note: • Only a minority of the 34 states with an autism insurance mandate varies benefits based on age. In fact, in recent years, states increasingly provide equal benefits without age caps. • CDC autism surveillance indicates the average age of diagnosis in the U.S. is 5.6 years. • The Asperger's diagnosis generally occurs much later: 7.2 years • Children from rural areas and ethnic minority backgrounds are at a particular disadvantage. Research shows that these families have to go to the doctor many more times before receiving a diagnosis, and the age of diagnosis is much older. Because of the substantial evidence that has been provided to you via testimony and public comment, we ask that you revise your recommendations and strongly recommend ABA interventions for people	All treatments, regardless of diagnosis, need to be individualized, yet that does not eliminate the need for public policy. State insurance mandates are not evidence, but are generally the result of a political process. The charge of the EbGS is to evaluate the evidence pertaining to ABA for the treatment of ASD. The cited ages at diagnosis are within the current recommendations for treatment. Recommendations for coverage of ABA only in those children ages 2 to 12 is a result of insufficient evidence of effectiveness of ABA in individuals older than age 12 based on the source report (Lounds 2012).

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		with autism spectrum disorder over the age of 12. As the HERC finalizes these recommendations, we ask that it carefully consider the real-world impact that the new rules will have on Oregon families in need of coverage. Thank you for your consideration of these comments.	
Q	1	I am writing to you on behalf of the myriad consumers over the age of 12 that are affected by autism. I am a Board Certified Associate Behavior Analyst and provide evidence based treatment (Applied Behavior Analysis) for individuals with autism between the ages of 2-16. As a behavior analyst I must adhere to the ethical guidelines of the Behavior Analyst Certification Board which states; *The behavior analyst promotes the general welfare of society through the application of the principles of behavior.* The application of the principles of Applied Behavior Analysis to treat socially significant behavior does not have boundaries or barriers regarding age, ethnicity, or any other variable that would suggest that socially significant behavior does or does not apply. Nor does socially significant behavior occur more frequently or intensely for a particular group of individuals. For a 3 year old it may be learning to talk rather than hit others to get his needs met. For an 8 year old it may be learning to be in a group rather than isolation. For a 16 year old it may be learning safety skills rather than taking a ride with a stranger. These are all socially significant behaviors that are necessary for individuals to be a part of our community, contribute to society, and remain safe in our culture. I have worked with individuals with autism for almost 20 years. I have had the opportunity to experience some of the most socially significant behavior changes in each and every individual I have worked with. I urge you to support ABA for ALL individuals. I strongly believe that it is everyone's ethical responsibility to consider and support all members of our community.	Thank you for taking the time to comment. The HERC process incorporates an evaluation of evidence as well as consideration of costs and public values and preferences in making decisions about coverage recommendations. There is insufficient evidence that ABA is effective in individuals over age 12.
R	1	While I do not live in Oregon, I wanted to write in my support of adding ABA coverage for inclusion in the "prioritized list" of treatments in the Oregon Health Plan. My own son is autistic, and the difference ABA therapy has made in his life is astounding. A little over a year ago (at the age of 2 & 1/2), my son was considered non-verbal and had a severe language delay. Last November, he started an intensive treatment program and received 24 hours of ABA therapy a week. In just a number of months, he begin speaking and now has a vocabulary of over 1,000 words. More than that, my son is learning the skills necessary to become an independent adult. I strongly encourage HERC to add ABA therapy to their prioritized list and that there be no minimum age. Children can be diagnosed as early as 18 months (my own son was diagnosed just after his 2nd birthday), and new medical breakthroughs are lowering the age constantly. Early treatment gives a	Thank you for your comment. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.

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		child the best chance for success. Additionally, while treatment at a young age is generally the most effective, patients over the age of 12 should still be given coverage for ABA therapy when medically necessary. Even at an older age, the quality of life, reduction of self-injurious behaviors, and skills gained can still be significant.	
S	1	Since January 2006, my son has received 30-40 hours of ABA per week. We chose ABA on the medical advice of our pediatrician, the long-standing research supporting ABA, and the experiences of other parents who saw positive outcomes for their autistic children using ABA. Because of a lack of service providers, we converted a bedroom into a playroom, outfitted it with supplies, secured a behavior consultant to oversee the program, and hired line therapists. We paid for it out of pocket, as Kaiser (our insurer at the time) offered no ABA. In 2008, Providence Health Plans began covering our son's program in accordance with an IRO decision that overturned its denial of coverage. It continues to pay for his ABA program to date. A little about our son: his development was on track until age 2.5. He was a beautiful toddler, speaking two languages, and showing interest in all the things typical 2 year olds enjoy. We were astonished and helpless watching this verbal, engaged child growing silent, lining up cars, or launching into a meltdown for no clear reason. Our primary concerns became to help him recover his language and relieve his obvious distress in a world that was now foreign to him. Data from those early days tracked the progress of our non-verbal, highly anxious child as he made progress on goals like eye contact, verbal imitation, expressive labels, gaining attention, and receptive commands. The progress was gradual, but we saw greater progress when we pulled our son from public school at the start of first grade so he could receive intensive ABA. Clinician treatment reports included assessments like these: • N. was observed to make eye contact more consistently and more spontaneously. When he doesn't provide eye contact spontaneously, he responds to a verbal prompt of "let me see your eyes" or "I need your eyes" within 1-2 seconds 90% of the time. When someone enters the room, he looks up at them 100% of the time. (1/21/08) • This Clinician was able to understand 17 words/phrases in a 2 and a half hour observation. It was observed that N.'s articulation decreased toward the end of the session when he was more tired. (1/21/08) • N. can sustain eye contact consistently on average for 5 seconds or more. He also makes shorter eye contact, but quite often and quite naturally. It's wonderful to see! (10/27/08) • When he is motivated and engaged, he will engage with a play partner for longer than 20 minutes.(10/27/08) • N. has also become more flexible as far as when he is requested to do something he does not	Thank you for sharing your story. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.

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		want to do, he may protest, but does give in without a problem. (7/20/08) • Modeling continues, but we are seeing longer sentences and spontaneous loops of conversation. For example, N. will ask, "Bob the Builder – sing!", "Go to Sauvie Island," or "I want car – airport – fly," which is especially exciting to hear. A majority of his language is comprised of three word sentences, so we continue to work on this goal. (8/31/09) • When engaged, N. can sustain eye contact up to 12 seconds. N. consistently sustains eye contact for about 7 seconds in 3 out of 5 opportunities, not quite 4 out of 5 yet. (6/9/10) • N. is using up to 6 word sentences, but consistently he is using 4-5 word sentences in 3 out of 5 opportunities, not quite 4 out of 5 yet. (6/9/10) • N. was observed to answer correctly "what" and "where" questions. He also answers questions with regard to "who." He stills struggle with answering "when" questions. He is making great stride with this goal!! (1/17/11) • N. appears to be very motivated by writing and drawing. He often requests for writing and drawing of logos like Target. Therapists are reporting they are able to fade the hand-over-hand prompt, and in some cases he can draw without HOH. (1/17/11) • N. is spontaneously asking "What is it?" when he wants to know about something. He is doing this at least in 3 out of 5 opportunities. (10/31/12) • N. consistently references others to share in his favorite activities, and he will do so with prompt if it is a new activity. N. also responds very well to subtle hints/cues from adults to share his activity. (10/31/12) • N. has learned to navigate [ProLoquo2Go], and use it to help express himself when he can't think of or say the word or phrase in the moment. (3/15/2012) • N. has a very strong understanding of language, and has demonstrated the ability to learn new skills with minimal training (trial presentations). He demonstrates the ability to organize himself within activities and requested behavior. N. also demonstrates sophisticated problem solving skills within preferred and non preferred activities. (3/15/12) • N. has developed an interest in his peer group, and is beginning to co-regulate among a small group of peers characterized by staying with the group, understanding when it is his turn or another's turn, and participating in activities. (9/15/13) I understand that the HERC is considering its recommendation re: coverage of ABA for children older than 12. I urge you to strongly support this coverage, as there is a subpopulation of children on the autistic spectrum like our son who will need ABA past this age. I can state with confidence that the majority of parents I know report that their autistic children do not require ABA past early childhood. However, denying coverage of ABA to those who do constitutes a cessation of medically-necessary	

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		services and is discriminatory. ABA has helped N. better manage the symptoms of autism, and is responsible for improving his quality of life and increasing independent skills.	
T	1	I applaud the Commission's recommendation of coverage for Applied Behavior Analysis for children aged 2-12 suffering from Autism Spectrum Disorder and urge the Commission to recommend coverage of ABA for older patients suffering from ASD. The Draft report which claims that there is insufficient evidence of the efficacy of ABA as a treatment for ASD for older patients relies on reports such as AHRQ and Hayes, the latter of which has been thoroughly discredited by several federal courts. The draft report discounts or fails to consider any study that has a fewer than 10 participants or does not randomly assign participants to study or control groups. However, decisions to deny coverage of ABA for ASD based on these same criteria have been found to be arbitrary and capricious and have been overturned by numerous federal courts which, in so doing, have rejected the argument that insufficient evidence supports the efficacy of ABA because few large studies or randomized studies have been done. Courts have recognized that ABA is the standard of care for autism spectrum disorder for patients of all ages, that ABA results in dramatic improvement in function for many of the individuals who receive it, and that no comparable alternative treatment exists when effectiveness and potential for harmful side effects are considered. Attached (see references) are several decisions from federal courts which overturn refusals to cover ABA for ASD and order coverage. I urge you to reconsider your recommendation against coverage of ABA for patients suffering from ASD who are older than age 12.	The Warren report includes study designs of all kinds that include at least 10 participants, not only those that use random assignment. Legal decisions are not evidence of effectiveness. The charge of the EbGS is to evaluate the evidence pertaining to ABA for the treatment of ASD. EbGS does not believe the evidence is sufficient to content that ABA is effective in individuals over age 12. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
U	1	I urge you to consider a broader range of evidence and expert testimony on the effectiveness of Applied Behavior Analysis and the full range of conditions it can treat. The draft report demonstrates that for an unknown reason this committee focused almost exclusively on ABA as it relates to early childhood intervention. That focus left out significant research showing that, among many appropriate applications of ABA, it represents the *only* behavioral intervention that has efficacy data in the treatment of severe problem behaviors in individuals with autism and/or intellectual and developmental disabilities (IDD) such as self-injury, aggression and pica. Please consider that the incidence of severe problem behaviors in individuals with IDD has been estimated to be 10% for the most severe behaviors (life-threatening) and to up to 40% when less severe behaviors are included (see attached Hagopian, et al.) These severe behaviors (self-injury, aggression, pica, etc.) lead to significant medical consequences for the individual, caregivers and family. Also, these behaviors are manifest in individuals of all ages throughout the lifespan. The current committee recommendation wouldn't help many (and perhaps most) of Oregonians suffering from these behaviors.	The HERC was given the directive in legislation to evaluate the evidence on ABA as a treatment for ASD; their charge was not to evaluate ABA for other conditions. The EbGS evaluation included review of a comprehensive report completed by AHRQ (Lounds 2012) on the effectiveness of treatments (including ABA) for individuals with ASD from ages 13 to 30.

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U	2	Our daughter's self-injury (she has autism, IDD and is non-verbal) was occurring at the rate of 600-900 times per day and included fist-to-head, knee-to-head, head to hard surfaces (tables, walls, floor) and head-butting to caregivers and family. When this behavior began at age 8, we sought treatment from neurologists, psychiatrists, occupational and physical therapists throughout the Pacific Northwest including OHSU and Children's Seattle. We ruled out underlying medical conditions and tried over 25 different psychiatric medications. Unable to safely care for her in our home with limited OHP/Medicaid funds, we were forced to make the wrenching decision to move her to an OHP funded group home when she was 11 years old. This group home had access to the best of Oregon's services for individuals with IDD and severe behaviors. After three years her self-injury was getting worse and she was so afraid of herself that she would cry and hit herself at a rate of over 40 times per minute unless she was wrapped in blankets and pillows from her neck to below her knees. Finally we sought help from the nation's most renowned inpatient program designed to help individuals like our daughter just last year when she was 15 years old - Kennedy Krieger Institute at Johns Hopkins in Baltimore, MD. Using a multidisciplinary approach and ABA principles allowed doctors to identify the function of her self-injury and target treatment to those functions. After a 5 month admission our daughter's self-injury was reduced by over 90%. Almost a year later she continues to have a successful behavior treatment program here in Oregon that was developed at Kennedy Krieger. She is happy, anxiety-free and no longer needs to be wrapped in blankets and pillows to feel safe from herself.	Thank you for sharing your story.
U	3	Please review the important evidence included in the following articles which articulate the medical necessity of treating problem behaviors and list the strong evidence which supports the efficacy of ABA. I can assure you that parents of children (both young and adults) suffering from problem behaviors would tell you that we can't give up on our children and we would be consigning them to a life of suffering from severe behaviors without access to ABA. We need you to understand that NO other behavioral intervention has been shown to be effective for our children. Matson, J. L., & LoVullo, S. V. (2008). A review of behavioral treatments for self-injurious behaviors of persons with autism spectrum disorders. *Behavior Modification*, *32*(1), 61-76. Hagopian, L. P., Rooker, G. W., Jessel, J., & DeLeon, I. G. (2013). Initial functional analysis outcomes and modifications in pursuit of differentiation: A summary of 176 inpatient cases. *Journal of Applied Behavior Analysis*, *46*(1), 88-100.	Matson is a descriptive review article of the kinds of treatment of SIB in individuals with ASD compared to those with intellectual disability (ID), finding much more research on the latter. Authors state, “Unfortunately, rarely are failed treatments, whether applied systematically or not, reported. And when they are noted, it is typically in a very cursory fashion.” Hagopian is a consecutive case series of 176 individuals with ID and severe problem behavior who completed functional analysis (FA) in an inpatient setting. Over half had ASD. The paper examines whether specific forms of modification lead to increased success in identifying the function of various problem behaviors. A function was identified in 86.9% of the 176 cases, and in 93.3% of the

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			161 cases for which the FA, if necessary, was modified up to 2 times. Also reports that differentiated outcomes ultimately were obtained for 86.9% of the 176 cases. EbGS added a recommendation for coverage of ABA for individuals 13 and older with specific problem behaviors.
V	1	We appreciate the effort that went into drafting the above-referenced report and the opportunity to comment on it. Unfortunately the report does not represent an evaluation of the evidence on applied behavior analysis (ABA) interventions for autism spectrum disorders (ASD) and should not be used to guide coverage decisions because The report mischaracterizes the discipline of behavior analysis, its research methods, and its applications in treating ASD. • Reviewers misidentified several interventions as ABA that do not have the defining characteristics of ABA. Consequently, many of the studies reviewed did not involve ABA interventions. • Reviewers did not consider evidence from the full range of scientific studies on ABA interventions for ASD. • Most of the scientific research on ABA interventions for ASD was excluded. Because the stakes are high, we strongly urge the HERC to revise its report with input from professionals with expertise in behavior analytic concepts, research methods, and applications to ASD. We offer the following to help guide the revision.	The commenter does not specify what interventions are misclassified. See comments #F2 and #N2 regarding rationale for limiting what research was considered.
V	2	**Behavior analysis** is a natural science that views behavior (rather than hypothetical entities like mental structures and processes) as its subject matter, and observable environmental variables as the principal causes of behavior. Behavior occurs only at the level of the individual, so **behavior analytic research** involves observing and measuring the behavior of individuals in relation to environmental events in the framework of single-case research designs (SCRDs). **These are not descriptive "case studies," but rigorous controlled experiments.** Behavior analytic research methods are **well-suited for evaluating many treatments for ASD**, which manifests behaviorally and affects each individual differently.	EbGS acknowledges this distinction.
V	3	In a typical ABA study, the target behavior is a skill to be developed (e.g., asking for help, completing a hygiene routine, cooperating with a medical procedure) or a maladaptive behavior to be decreased (e.g., self-injury, wandering, consuming inedible items). Many studies involve more than one behavior and participant. Each behavior is defined in observable terms and measured in repeated sessions	EbGS is aware of SSRD and that these can be considered controlled trials. See comment #F2 for limitations of SSRD.

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		under baseline (control) conditions without the treatment of interest in place, and with the treatment in effect (the experimental condition). Treatment procedures are environmental events that are arranged to precede (e.g., prompts, cues) and/or follow (e.g., reinforcers) occurrences of the behavior close in time. Baseline and treatment phases are repeated with the same individual and/or other participants. Graphed data are analyzed to determine if a treatment produced clinically meaningful improvement in comparison to baseline or another treatment procedure**.** That is, **ABA studies are controlled clinical trials (CCTs)** in which each participant experiences the control and treatment conditions, and comparisons of those conditions are replicated**.** Thousands of peer-reviewed studies have evaluated ABA procedures for building skills and reducing problem behaviors in many clinical and non-clinical populations in a wide range of settings.	Total number of citations provided, including legal decisions and guidelines, totaled 337.
V	4	Well-designed ABA CCTs produce rich information about behavior change procedures and individual responses to treatment that cannot be derived from most studies using between-groups research designs with statistical analyses of group averages and other mathematical abstractions. The **generality (external validity)** of ABA interventions is demonstrated empirically with replications, rather than by speculating about whether study samples represent populations. Many ABA CCTs have been conducted in homes, schools, and community settings, which strengthens their generality.	SSRD are by definition not generalizable to populations. EbGS agrees that generalizability is improved by replication, as referenced in proposed standards outlined in comment #F2.
V	5	In practice, ABA interventions comprise ***focused interventions*** using a small number of procedures to address a small number of treatment targets to be increased (e.g., following instructions, completing hygiene routines, cooperating with medical procedures) and/or decreased (e.g., self-injury, wandering, consuming inedible items), or ***comprehensive interventions*** in which many procedures are used to address multiple targets. Decisions about specific procedures as well as the intensity and duration of treatment are based on scientific research, professional knowledge, direct behavioral observations, and the characteristics, needs, and preferences of the individual client and his/her family.	EbGS acknowledges this. EbGS decided that intensive interventions are appropriate for ages 1-12 and targeted interventions are appropriate for all ages.
V	6	Specific **recommendations for revising the draft HERC report** are: Delete studies and reviews of interventions that do not have the defining characteristics of ABA *as verified by professional behavior analysts with experience in designing, overseeing, and studying focused and comprehensive ABA interventions for ASD.*	The commenter does not specify what these are.
V	7	Clearly distinguish focused and comprehensive ABA interventions, and consider the scientific evidence on each from ABA CCTs as well as group design studies involving people with ASD *of all ages.*	Both focused and comprehensive interventions were eligible for inclusion in the Warren report. See comment #Y6.

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V	8	Review the documents in the attached reference list for scientific evidence about the effectiveness and risks of ABA interventions *in comparison to no intervention and other interventions, as required by the HERC Guidance Development Framework.* The documents include: • Technical reviews conducted by teams that included expert behavior analysts and used standardized protocols for evaluating SCRD studies as well as group-design studies. Those reviews meet a HERC criterion for high-quality evidence (evidence-based guidelines from trusted sources). • Systematic reviews, meta-analyses, and other analyses of data from multiple ABA CCTs of focused ABA interventions for behaviors that directly affect the health, safety, and overall functioning of people with ASD. Several meta-analyses demonstrate methods of aggregating data across many SCRDs to yield evidence of both statistically and clinically significant effects with large Ns. Those sources meet HERC criteria for high- or medium-quality evidence. • Two meta-analyses of data from studies of early intensive ABA intervention by Eldevik and colleagues. Those authors included only studies in which the ABA intervention had characteristics on which behavior analysts who design and study such intervention agree. Their 2010 meta-analysis, which used individual participant data from 16 group-design studies, provides the strongest available evidence on the effects of bona fide intensive ABA in comparison to standard interventions for young children with ASD.	The technical reviews include one of 2 evidence reviews commissioned to inform the NZ guideline on the treatment of autism, the NAC NSR (see comment #G2) and the New York state guideline (see comment #I5). See evidence table for SRs and MAs (total of 26 citations). Eldevik 2009 was limited to EIBI (ages 2-7), included 34 studies, 9 of which were controlled, and calculated effect sizes for intelligence and adaptive behavior that are considered moderate to large. Eldevik 2010 had similar inclusion criteria and assessed individual patient level data. Results found reliable change in IQ in 30% of the treatment group compared to 9% for control, and reliable change in adaptive behavior of 21% compared to 5%. These support the current recommendations in the evidence evaluation.
V	9	Describe the quality of evidence on focused and comprehensive ABA interventions for children ages 0 – 12 years as "high," and strengthen the rationale for the strong recommendation for coverage.	The EbGS has made a strong recommendation for coverage in this population, despite low strength of evidence.
V	10	Strongly recommend ABA interventions for people with ASD over the age of 12 because the quality of evidence is medium to high, there are few other safe and effective interventions, and depriving people with ASD of effective ABA interventions puts their health and safety at risk and increases costs for their healthcare and other services.	For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
W	1	Most people, parents, clinicians, and most certainly insurance company administrators, do not understand ABA or how it works to improve function in children with autism. In my opinion, most ABA professionals have done a poor job of explaining it. Sometimes they describe what they do using lots of jargon and scientific-sounding terms that are off-putting to policy makers and parents alike. I too was unsure about the technique until I worked closely with BCBAs and other practitioners and children and saw first-hand the strides children make when receiving ABA therapy. The HERC should listen with an open mind to the many success stories it will hear.	Thank you for these comments. This public comment process is a reflection of HERC's commitment to hear all perspectives. Our process used to develop this evidence evaluation includes public comment as well as an evaluation of the evidence.
W	2	Not all children require ABA therapy. It will not be medically necessary for many children. It is best	Thank you for these helpful, concrete insights and recommendations. Some of these recommendations are

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		used with those who: • Have unsafe and/or self-injurious or aggressive behaviors • Are non-compliant with simple parental instructions (“come here”, “sit down”, etc.) • Are still living in the home with their parents • Have parents who are invested in learning the technique and support therapy at home • Have parents who comply with all attendance requirements ABA will not be effective if a child does not receive regular and frequent visits with their therapists, working on the identified “programs”. With ABA quantity is as important as quality. Our clinic required 3 to 5 days of attendance per week. Children progress much more quickly when they get in the routine of coming to clinic and “going to work” on a regular basis. Using ABA, children can be taught to participate in their own health care. For example, our therapists taught children to swallow pills, thereby improving compliance with their medication regimens. We taught them to be tolerant of a wider range of foods, thereby improving nutrition. We taught them to use the toilet and wash their hands, reducing the spread of germs and diaper rash as well. (remember, many of our autistic teens are still in diapers.) We taught overweight children how to reduce their fear of playing on a playground, thereby improving mobility. We taught "car seat Houdinis" to stay buckled in the car seat, thereby reducing the risk of accidents by distracted parents. We taught non-verbal children how to ask for help. All humans deserve the ability to ask for help. ABA therapy can be life saving. A child who cannot respond to simple demands such as "stop" "come back" or "no!" is a danger to himself and others. ABA helps break the autistic "bubble" that prevents children from complying to their parents' instructions. Anyone who has ever parented a young, stubborn two-year old, can relate, then, to the difficulty of trying to stop a 12 or 15 year old young man from running into traffic or jumping into a pond. A child who has, through discrete trials, learned to STOP on command is a safer child. * For best results, children should be served by programs who assign multiple practitioners to each child. A good treatment plan includes the rotation of therapists to encourage flexibility in routine and generalization of skills, both of which are difficult for kids with autism. The majority of hours spent in “table time” need not be provided by a BCBA, but rather by trained paraprofessionals with oversight by BCBAs. Funded agencies must adhere to supervision standards to ensure that paraprofessionals are conducting. It is essential, however, that a BCBA oversee the programs and know when to "push" the child to the next level of competence. Programs should be	implementation issues and are more specific than what is required for the purposes of this evidence evaluation.

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		challenging to children and therapists must never let children rest on their laurels too long. We used to tell parents that "when a child has autism, he has to get to work earlier and stay later, because their work load is bigger." ABA works. The best evidence is provided by parents who have seen their children become functional after years of dysfunctional, unhealthy behavior. Let me share a quick story about my child who is 25 years old and now a college graduate. She was non-verbal. I grieved her inability to speak and feared one thing more than another: That my daughter would not be able to say the word "no." "How can a child protect herself," I wondered, "if she can't say "NO. Through the efforts of a very talented speech therapist who utilized an ABA-based approach in a medical setting (a stroke rehabilitation clinic at the Riverside Community Hospital) my daughter learned to talk.	
X	1	As a professional who provides ABA treatment to individuals with autism in Central, Southern, and Eastern Oregon, I would like to submit my comments on the HERC draft evaluation of the evidence for ABA. The HERC findings have very important implications for citizens in Oregon who are affected by autism, particularly for those vulnerable individuals served by the Oregon Health Plan. It is vital that we meet the needs of these individuals by affording them the same medically necessary behavioral health treatments that are available to others in the state. I am pleased to read the strong recommendation for coverage of comprehensive ABA services for children with autism ages 2-12. However, I strongly urge that HERC revisit the finding that the evidence supporting comprehensive ABA is low, as well as the age restriction against ABA for children under age 2. Additionally, I strongly urge that the commission review the recommendation against coverage of ABA interventions for older children and adults, as well as the finding that the quality of the evidence is weak for these interventions.	Thank you for your comment.
X	2	In drawing conclusions about the evidence for ABA interventions, it is imperative that the HERC review not be limited to randomized controlled trials (RCTs) and comparative effectiveness reviews. Because RCTs are often unethical or not feasible with this highly individualized, often long-term treatment for a vulnerable population, it is essential that other kinds of experimental designs and evaluations be considered. As shown in the attached reference list, there are many trusted sources that have concluded the evidence supporting ABA is strong. Additionally, under its own process framework, HERC is obligated to consider a variety of kinds of evidence, such as peer-reviewed studies, guidelines published by professional organizations, and cost-benefit analyses. In particular, there are a number of meta-analyses of single subject experimental research designs that provide	The evidence evaluation is not limited to RCTs and comparative effectiveness reviews; see comment #L3. RCTs have been conducted and are included in the evidence; hence EbGS does not believe they are not feasible or ethical. A number of other experimental designs are also included. HERC is not obligated to consider a variety of kinds of

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		evidence of ABA's effectiveness across age ranges and symptoms. Furthermore, the commission must reexamine the literature supporting focused ABA interventions. While RCTs of these interventions are not available because of the nature of the treatment and severity of symptoms, there is an abundance of single case research studies and meta-analyses supporting focused interventions. While much of my practice involves comprehensive ABA or EIBI, a significant portion of my clinical practice also involves using focused interventions to treat severe challenging behaviors. This work is critical for families, because it addresses symptoms that are extreme and can be life threatening. For example, elopement, or running away, is a common behavior among individuals with ASD, and one that poses a significant risk due to safety hazards such as drowning or traffic accidents. Research in focused interventions supports functional behavioral assessment and function-based treatment of elopement (e.g., Lang et al., 2009). In my clinical practice, I have used focused interventions to treat elopement, and it has been essential to the day-to-day well being of patients and the functioning of families.	evidence, but in the case of this evidence evaluation, has included a number of different types of evidence, including RCTs, cohort studies, case series and SSRD. They also consider values and preferences and resource implications, as noted in the GRADE table. Lange 2009 is a SR of SSRD evaluating treatments for elopement. It included 10 studies and 53 participants, of which 6 had ASD. Only 5 of the 10 studies utilized an experimental design, and the authors state: "the existing literature base is perhaps best described as limited with respect to the overall scope and quality of the existing corpus of studies" and "In terms of methodological quality, perhaps the most important limitation is that many of the studies appeared to lack a recognized experimental design. Thus the reports of positive outcomes for 80% of the studies must be interpreted with caution."
X	3	Another way in which focused interventions may improve the health and well being of patients is by teaching tolerance for medical procedures. In my practice, I often implement interventions designed to improve behavior during dental cleanings or medical procedures. For example, if a patient is taking a medication that requires regular blood draws to monitor organ functioning, it is essential that the patient tolerate needles. Often, individuals who do not have access to this kind of focused intervention must be restrained or sedated in order to receive routine dental and medical procedures. The literature supports focused ABA as an effective means of teaching individuals with autism and other developmental disabilities to tolerate important medical procedures (e.g., Shabani & Fisher, 2006). There are many more examples of ways in which focused interventions can improve the health, well being, and safety of individuals with ASD, and it is vital that this literature be considered, given the nature of symptoms and the implications for those who are in need of this type of treatment.	Shabani 2006 is SSRD report of one participant whose needle phobia was treated successfully with stimulus fading and differential reinforcement.
X	4	I strongly recommend that you work with the ad-hoc ABA expert, Dr. Eric Larsson, to revisit the body of literature evaluating ABA. In doing so, it is vital that Dr. Larsson be allowed to assist in identifying studies for which the intervention procedures were truly behavior analytic, so that studies that do not meet the standards of the field may be excluded. Additionally, Dr. Larsson can help the commission	See comment #Y2. Testimony by Dr. Larsson and the other (non-appointed) experts is addressed in this document (Dr. Green and

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		better understand the various interventions that meet criteria to be considered ABA, in particular distinguishing between comprehensive versus focused interventions. Given the very different aims and parameters of these two categories of intervention, it is important that the evidence for each be considered separately. Finally, it will be important to carefully consider the information and sources provided by other experts who have testified before the commission, including Dr. Gina Green of the Association of Professional Behavior Analysts, Dr. Louis Hagopian of The Kennedy Krieger Institute, and Dr. Brian Reichow of Yale University.	Reichow), and references provided by Dr. Hagopian are included in the evidence table. We have not received requests to remove any specific studies from the evidence evaluation because they do not pertain to ABA.
X	5	I urge you to maintain your strong recommendation in favor of coverage of comprehensive ABA treatment for children through age 12, but remove the minimum age limit of 2 years. Given the multitude of sources supporting ABA, including reviews by trusted sources, peer reviewed studies, and guidelines from professional organizations, the quality of the evidence should be revised to "high." This recommendation from HERC will enable young children with autism to receive appropriate, comprehensive behavioral health treatments that will help many children to achieve functioning in the normal range, saving significant costs long term. Furthermore, I urge you to revise your recommendation regarding focused interventions for older children and adults. Based on the HERC's standards, the quality of evidence for these interventions should be rated as "medium" at minimum. Given the importance of these interventions to the health and well being of individuals with autism, as well as the risks of not treating certain symptoms, the recommendation should be "strong" in favor of coverage.	It is unclear why the evidence for older individuals should be rated as "medium". For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
Y	1	The Oregon Association for Behavior Analysis Board has reviewed the HERC draft coverage guidance for ABA. We have several concerns that we ask that you urgently address. First, we ask that the commission members work with experts in behavior analytic research methods and intervention procedures to better understand the evidence on ABA interventions and to address key concerns with the sources relied upon for the draft report. Specifically, 1. Many interventions that were reviewed for the draft report are not in fact ABA interventions. The result is a misleading picture of both the nature of ABA interventions and the evidence of their effectiveness. To establish valid criteria for inclusion and exclusion of studies for review, the commission should consult the ad-hoc expert in ABA, Dr. Eric Larsson.	See comment #X4
Y	2	2. The commission must also work with Dr. Larsson to better understand the full range of ABA interventions and the scientific evidence on their effectiveness. Those interventions may be categorized as follows: a. Early intensive ABA and other **comprehensive ABA intervention** models involve 26-40 hours per week of intensive intervention in which multiple ABA procedures are used to address	Thank you for providing a definition of comprehensive vs. focused ABA. However, since both categories still can include multiple treatment goals and the hours per week can vary for focused ABA, presumably above 25 hours in some cases, the distinction still remains unclear.

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		multiple treatment goals and symptoms. The best meta-analyses of controlled group-design studies on bona fide early intensive ABA indicate that when it is designed and overseen by qualified behavior analysts and delivered for at least 30 hours per week for at least two years, it is effective for producing large improvements in many children with autism who begin intervention before age 8, and more modest but still clinically significant improvements in many others. Contrary to the HERC draft guidelines, there is no indication that comprehensive ABA intervention is ineffective for children younger than 2 years or older than 8 years; in fact, most of the procedures that comprise comprehensive ABA intervention have been shown to be effective in thousands of replicated ABA controlled clinical trials. b. **Focused ABA interventions** address small numbers of specific treatment goals and symptoms, including targets that directly affect the safety, health, and overall functioning of people with autism of all ages. The number of hours of intervention per week and the duration of intervention varies with the nature and severity of the individual client's treatment targets, level of functioning, life circumstances, and other factors. Procedures used in focused ABA interventions have been proved effective in thousands of replicated ABA controlled clinical trials involving people with autism ranging from young children to adults. Many studies of focused ABA interventions have been aggregated and analyzed in high-quality technical reviews, systematic reviews, and meta-analyses overlooked in the HERC draft report. In overlooking the evidence on focused ABA interventions, the commission risks depriving many individuals with autism of effective treatment.	The evidence source included interventions that may be defined as comprehensive and focused ABA. The optimal duration and intensity of comprehensive type interventions versus focused, and even a fully implementable distinction, is unclear. The current recommendation for coverage of ABA between ages 1 and 12 would allow for coverage of both. Whether there should be differing requirements for ongoing evaluation and proof of individual efficacy will need to be addressed. With regard to children under 2, the primary evidence source (Warren 2011) found insufficient evidence to determine efficacy; see comment #N4. However, the lower limit was changed to age 1 in response to expert opinion. The draft evidence evaluation does not state that ABA is ineffective for children older than 8. Citations not specified. See evidence table. Commenter provided 20 references.
Y	3	3. The review must include evidence on ABA interventions from studies using a range of sound scientific research designs rather than just the results of randomized clinical trials (RCTs), other studies using between-groups research designs with statistical comparisons of group mean scores, and comparative effectiveness reviews. Although RCTs and inferential statistics are appropriate for addressing some important research questions about some treatments for some populations, they have ethical, practical, and other constraints that limit their utility for evaluating certain types of treatments for certain disorders and conditions. A number of other research methodologies are better suited for answering questions about the direct effects of treatment procedures on behavior, and the effects of many types of treatments on individuals. We urge the commission to review the attached reference list in revising the current draft, with guidance from Dr. Larsson. The list includes sources that are considered "high quality" by HERC	The evidence evaluation does include a broad range of research designs. See evidence table. See comment #I6.

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		standards, including systematic reviews of controlled clinical trials that used a range of research designs, and evidence reviews by teams that included expert behavior analysts. It also includes several "medium quality" sources, such as well-conducted peer-reviewed studies and meta-analyses. We also ask the commission to consider the recommendations of professional societies, such as the American Academy of Pediatrics, and the oral and written testimony of expert behavior analysts Dr. Gina Green, Dr. Louis Hagopian, and Dr. Brian Reichow.	
Y	4	Second, we ask that the commission work within the framework set by HERC. Specifically, • The commission is obligated to consider sources other than RCTs and comparative effectiveness reviews (ORS 414.701), the full range of peer reviewed literature (ORS 743A.062), and evidence related to clinical and cost-effectiveness (ORS 414.690(3)).	For clarification, the statutes cited were established by the legislature, not HERC. See comment #L3 regarding comparative effectiveness. ORS 743A.062 defines peer reviewed literature as "scientific studies printed in journals or other publications that publish original manuscripts only after the manuscripts have been critically reviewed by unbiased independent experts for scientific accuracy, validity and reliability. Peer-reviewed medical literature does not include internal publications of pharmaceutical manufacturers". ORS 414.690 states that the HERC "Shall consider both the clinical effectiveness and cost-effectiveness of health services, including drug therapies, in determining their relative importance using peer-reviewed medical literature as defined in ORS 743A.060". EbGS believes that they have met these requirements.
Y	5	• Based on the HERC Guidance Development Framework, there are many paths to a "strong" recommendation. It is important that the commission consider other factors in addition to the published evidence, such as the availability of alternative treatments, the risks and benefits of treatment, the prevalence of the treatment, and the feasibility of clinical research study.	The Guidance Development Framework does not determine the final recommendation, but rather is used by HERC as a guide. That said, EbGS has considered other factors in addition to the published evidence, which is how the current recommendation for children 2 to 12 is strong rather than weak, which is the rating that would have been provided had patient preferences not been considered.
Y	6	We are pleased that the commission is making a strong recommendation for coverage of ABA for	The evidence evaluation is not a guideline; it is an

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		children age 12 and under, but we have grave concerns about the other conclusions the commission has reached. After considering the factors just described, the commission should conclude that • The quality of the evidence is *high* for comprehensive ABA intervention for children age 12 and under, and the commission should make a strong recommendation in favor of coverage of ABA for children age 12 and under *with no minimum age limit*. • The quality of the evidence is *moderate* to *high* for focused ABA interventions for people with autism of all ages, and the conclusion should be a *strong* recommendation in favor of coverage. • Because ABA is a highly individualized approach, coverage should be based on individualized assessments and recommendations made by qualified professional behavior analysts, rather than a generic guideline. The HERC coverage guidance on ABA has important implications for Oregon's most vulnerable residents. It would be unfortunate if an overly restrictive review process resulted in limited access to vital therapeutic interventions for individuals on the Oregon Health Plan, when across Oregon and the nation others are benefiting from improved access to medically necessary, evidence-based ABA interventions. Thank you for addressing our concerns.	evaluation of the evidence with recommendations for coverage for the OHP. As such, it is a policy document, and does not provide specific guidance for individuals. However, the coverage recommendation does contain a requirement for individualized treatment and periodic evaluation in order to ensure that services provided benefit the patient. See comment #H2. There is no distinction made in the core sources, nor in the public comments received, to distinguish which studies involved comprehensive vs. focused ABA in order to make a separate recommendation. For individuals older than age 12, EbGS has recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
Z	1	I commend HERC for recommending coverage of ABA for young children. I hope that HERC will change its recommendation for older patients. Unfortunately, the Draft Evaluation of Evidence on Applied Behavior Analysis for Autism Spectrum Disorders ("the Draft") indicates that crucial information submitted to HERC has not been considered, and the Draft does not reflect adherence to HERC's published process or processes.	EbGS disagrees that the draft evidence evaluation does not reflect adherence to HERC's process. Public comment that is submitted is addressed in this document and in the evidence table. See comment #H2.
Z	2	1. The Draft characterizes the strength of evidence as "low" in contradiction of its own process and without any explanation whatsoever. The Draft Evaluation characterizes the quality of the evidence supporting both EIBI and other ABA interventions for young children as "low." The Draft claims that the HERC has made its own assessment of the quality of the evidence, but that assessment is not described in the document, and the "low" assessment contradicts HERC's published process. The only discussion of strength of evidence in the Draft comes from the source documents and characterizes strength of evidence as low because there are relatively few randomized controlled trials. However, nothing in HERC's stated process permits HERC to assess the strength of the evidence	See comment #H2. EbGS disagrees that the "low" assessment of the strength of the evidence contradicts the HERC processes. EbGS used the strength of evidence evaluation of the Warren report, and also reviewed additional studies identified in the Maglione update. Rationale for strength of the evidence is given on page 14: "Given the small sample sizes in most trials and the diversity in

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		based on the number of randomized controlled trials or even the size of studies. HERC's Biennial Report, presented to the autism community as an official statement of HERC's process and attached, states that systematic reviews of prospective cohort studies and evidence-based guidelines from trusted sources are "high" quality. According to the same document, medium quality evidence sources include guidelines issued by professional societies and advocacy organizations (e.g. American Heart Association), coverage decisions by private health plans, and well-conducted, peer-reviewed individual studies (experimental or observational).	interventions, it seems likely that the overall strength of the evidence remains insufficient to accurately draw conclusions about the effectiveness of parent training programs." And for Key question #2, "This suggests that the overall prior conclusions that there is insufficient strength of evidence to evaluate the impact of provider type on efficacy of the intervention remain valid."
Z	3	Much of the evidence summarized in the draft qualifies as high and medium quality evidence. One example is Maglione, which is a systematic review of prospective cohort studies and therefore is high quality evidence. Maglione recommends coverage for ABA. Submitted herewith are a number of opinions from federal district and appellate courts ordering coverage. Members of the public have submitted dozens or hundreds of peer reviewed studies, all demonstrating the efficacy of ABA. All of this is high or medium quality evidence under HERC's published criteria.	See comment #H2, #J2 and #V3.
Z	4	GRADE assesses quality of evidence based not on the specific type of evidence considered, but rather on the likelihood that future research will change the confidence in the estimation of effect. However, the Draft includes no analysis whatsoever about the effect of future research on the estimation of effect. In fact, decades of ABA research all indicates that ABA is generally effective, and future research is extremely unlikely to change confidence in the estimation of effect. Therefore, under GRADE, the quality of the evidence is high.	EbGS disagrees that the quality of evidence is high. The Warren report uses similar methodology to GRADE (described on page 27 of the report), and found the strength of evidence for children 2-12 low. The description of low strength of evidence is that further research is likely to change the confidence in the estimate of the effect and is also likely to change the estimate.
Z	5	<u>2. HERC's Guidance Development Framework requires a recommendation of coverage for ABA for adolescents and adults.</u> Even though Drs. Hagopian, Green, and Riechow presented evidence of the efficacy of ABA for older patients at the September meeting, the Draft mischaracterizes the evidence of efficacy for older patients as consisting of only one poorly designed case study. HERC appears to have ignored the evidence cited by these experts. If that evidence is considered, there is sufficient evidence of the efficacy of ABA to recommend coverage for patients over age 12. Additionally, HERC's Guidance Development Framework requires a recommendation of coverage regardless of the sufficiency of evidence because denying patients access to ABA results in serious disability. HERC was presented with video and testimonial evidence from a family whose daughter	See comment #H2 and #H4. While appreciated, EbGS does not consider the experience of a single individual as evidence. See evidence table and comments #H3 and #U3 for comment on Dr. Hagopian's testimony.

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		experienced incapacitating disability as a result of self-injurious behavior, and which was alleviated through ABA. Testimony from Dr. Hagopian also provided ample evidence that ABA is used in older patients to resolve life and health-threatening behaviors which are otherwise profoundly disabling. However, the Draft disregards that evidence without discussion. Had HERC considered that evidence, it could not have found that "clinical research study is reasonable" and its Guidance Development Framework would have directed a recommendation of coverage for older patients even in the absence of "sufficient" evidence.	
Z	6	3. The Draft relies exclusively on comparative effectiveness research ORS 414.701 forbids HERC from relying exclusively on comparative effectiveness research in developing coverage guidelines. Despite this specific statutory prohibition, the Draft relies exclusively on comparative effectiveness research. Moreover, even though HERC was presented with a variety of forms of evidence, the Draft includes only comparative effectiveness studies with ten or more participants, and it prioritizes studies in which participants are randomly assigned to control and study groups. In other words, it not only relies exclusively on comparative effectiveness research, it relies exclusively on a narrow category of comparative effectiveness research. Other evidence was presented to HERC in the form of extensive written and verbal testimony from ad hoc experts and other witnesses. However, no mention of any of that evidence is made in the Draft, suggesting that it was ignored.	See comment #L3.
Z	7	4. The Draft misinterprets the research ABA (as defined by SB 365), and particularly EIBI is the standard of care for children with autism. For that reason, researchers studying interventions for children with autism spectrum disorders generally compare different ABA-based interventions. They do not compare a group of children who receive ABA against a group of children who receive no intervention, and they certainly do not through random assignment to a control group deprive children of their once in a lifetime opportunity to receive ABA based early intensive intervention. This was explained to the committee, but the Draft nevertheless misinterprets many of the studies summarized as comparisons between a study group that received ABA with a control group which did not receive ABA. In reality, many of the control groups in the summarized studies received a different type of ABA-based intervention, and it is unclear that some study groups received ABA-based interventions. The draft was prepared by individuals who have no expertise in behavioral healthcare, autism, or ABA.	EbGS agrees that many of the included studies compared ABA interventions to eclectic or other interventions, including community services and speech and occupational therapies. This does not negate their findings. The evidence evaluation was based on the Warren report, which utilized a technical expert panel; see comment #N3.
AA	1	I am writing to request that you decide to have OHP cover ABA therapy for children with autism, for those under and over the age of 12, equally and fairly. They need it. My 14 year old son, Scott, has autism and PANDAS (rheumatic fever of the brain). He is verbal and needs more ABA therapy to help	Thank you for your comment. For individuals older than age 12, EbGS has

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		him socially and academically. We have been waiting to resume it until we can get insurance to cover it. We have been paying as much as we can afford to out of pocket over the years. Insurance really ought to cover it, as they cover cancer treatments for people of all ages. Children with autism, etc., under and over the age of 12 deserve good, appropriate treatment too. ABA has been proven to be an effective approach in children of all ages. We have a doctor's note saying it's medically necessary for our son. There are others in our situation who receive good ABA coverage from their insurance companies without question, especially those who work for Intel and Microsoft. I would think OHP and the remaining insurance companies who don't cover it would step up and do the same, in OR and all other states. Most states now mandate it, and I know Governor Kitzhaber signed legislation mandating coverage for it in Oregon several weeks ago. Please require that OHP cover ABA therapy for patients both under and over the age of 12. It's very important to many families in Oregon.	recommended that targeted behavioral interventions be covered for up to 8 hours/month, for up to 6 months, to address specific problem behaviors.
BB	1	I respectfully request that you consider additional evidence in determining the effectiveness of applied behavior analysis for treating individuals with an autism spectrum disorder (ASD). In this letter, I will summarize the limitations of primarily considering randomized controlled trials in determining the effectiveness of ABA-based interventions for this population. Thereafter, I will describe the benefits of including data on focused interventions which provide a more accurate depiction of the evidence for applied behavior analysis. Finally, I request that the HERC Committee include evidence from experts in the field of applied behavior analysis in their report.	Thank you for your comments.
BB	2	**Limitations of randomized controlled trials** Although RCTs are beneficial for comparing the effects of intervention to a waitlist control group, this type of design can be challenging to use in certain populations. For example, school-age children with an ASD receive some type of intervention through their Individualized Education Plan (IEP). Because many children with an ASD are exposed to some type of behavior analytic intervention in their federally-funded educational programming (e.g., visual schedules, token reinforcement systems, functional communication training), it can be challenging to include these children in a true control group. Furthermore, there are ethical concerns related to withholding an effective intervention for children with an ASD, because IDEA mandates that children receive a free and appropriate education that includes some type of intervention. Thus, it can be challenging and unethical to arrange for a no-intervention control group for individuals with an ASD. The same considerations should be applied to certain ABA-based interventions for individuals with an ASD who would be exposed to dangerous or life-threatening symptoms if treatments were withheld. For example, adolescents who engage in severe self-injurious behavior that results in detached retinas, severe head injury, and broken bones (e.g., Kurtz et al., 2003) or life threatening	EbGS acknowledges the difficulties described here. RCTs and cohort studies have been completed and are included in the evidence reviewed in the evidence evaluation. Some of these included waitlist control, others included other (eclectic) interventions. With regard to SIB, it is assumed that the control group would be treatment as usual, which is currently covered by the Prioritized List.

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		feeding disorders (c.f., Kodak and Piazza, 2008) cannot be placed in a waitlist control group to evaluate the efficacy of an ABA-based, focused intervention because withholding treatment could result in further injury or death. As such, the field of applied behavior analysis relies on alternative study designs that allow for a demonstration of experimental control while minimizing the potential for harm to the participants.	
BB	3	**Alternative study designs and focused interventions** Single-case designs are frequently used in the field of applied behavior analysis to demonstrate functional (causal) relationships between independent and dependent variables. Although single-case design is often mistaken for poorly designed experiments with a single participant, single-subject research methods actually provide a level of experimental rigor that exceeds those of more traditional case studies (Horner, Carr, Halle, McGee, Odum, & Wolery, 2005). Because of the rigor of single-subject research methods included in behavior-analytic studies, these methods are now published in studies in 45 professional journals across fields (American Psychological Association, 2002).	Horner reference is the one previously described in comment #F2, which suggests standards for considering an intervention evidence based.
BB	4	The extant literature on the efficacy of ABA-based interventions for individuals with an ASD using single-subject research methods is immense. For example, Matson, Benavidez, Compton, Pacwalskyj, and Baglio (1996) noted that there are 550 behavioral studies conducted with individuals with an ASD. To ignore this entire body of research would be tantamount to negligence. In particular, there are a plethora of studies demonstrating the effectiveness of ABA-based interventions for children and adolescents with an ASD that do not evaluate early intensive behavioral intervention (EIBI). The HERC appeared to focus the majority of their review on evidence for EIBI, despite that fact that those studies represent only a small portion of the overall body of evidence on the effectiveness of behavior analytic interventions for children with an ASD. Focused (or specific) interventions based on the principles of applied behavior analysis such as functional communication training (e.g., Tiger, Hanley, & Bruzek, 2008), choice (e.g., Fisher & Mazur, 1997), extinction (e.g., Lerman & Iwata, 1996), punishment (e.g., Lerman & Vorndran, 2002), receptive and expressive identification training (e.g., Petursdottir & Carr, 2011), and teaching joint attention and symbolic play (e.g., Dube, MacDonald, Mansfield, Holcombe, & Ahearn, 2004; Wong, 2013) to name just a few, are shown to reduce problem behavior and/or treat core symptoms associated with an ASD. I encourage the HERC to include studies using single-subject research methods in their review of the evidence for applied behavior analysis for individuals with an ASD.	Thank you for providing specific references. Matson 1996 is not available without purchase. HERC utilized the inclusion criteria of the Warren report; see comment #N2 for rationale. Tiger 2008 is a systematic review of functional communication training with recommendations for practice. It includes 204 individuals, 81 of whom had ASD. Fisher 1997 is a narrative review of choice responding, including an evaluation of the differences between basic science, applied and bridge studies. Lerman 1996 is a narrative review of operant extinction, including both basic and applied research.

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			Lerman 2002 is a narrative review of punishment for the treatment of behavior disorders, including both basic and applied research. Petursdottir 2011 is a narrative review of the impact of the sequencing of instruction for receptive and expressive language in EIBI. Dube 2004 is a narrative review and a "contingency analysis of gaze shift in joint attention initiation". Wong 2013 is a RCT evaluating a classroom-based intervention and compared the order in which preschool teachers were exposed to 2 different interventions, 1 symbolic play and the other joint attention. Both were effective for increasing these attributes when compared to baseline and to waitlist control.
BB	5	Focused interventions based on the principles of applied behavior analysis that use single-subject research methods to treat specific, life-threatening behavioral concerns are of critical importance to review. For example, approximately 10%-14% of individuals with mental retardation display chronic self-injurious behavior (Kurtz et al., 2003). Yet, few interventions, other than those based on applied behavior analysis, produced reductions in this severe behavior. Behavior analytic interventions based on the individual's function of self-injurious behavior have been shown to substantially reduce self-injurious behavior (e.g., Iwata et al., 1994) for individuals with developmental disabilities, including individuals with an ASD. Therefore, it is critical to include a review of focused interventions based on ABA in the HERC report.	Iwata 1994 is a consecutive case series of 152 individuals with SIB (number with ASD not specified). 74 were over aged 20 and an additional 39 were between 11 and 20. Authors analyzed reinforcing functions of SIB and concluded that functional analysis is extremely effective in identifying the environmental determinants of SIB (successful in 95% of cases) and therefore guiding treatment selection. Also reported that the interventions of extinction, differential reinforcement and punishment were effective in significantly reducing SIB in over 80% of cases. For those individuals in which EIBI is not indicated (for example., SIB), EbGS recommends that less intensive behavioral ABA-based interventions be covered to address specific problem areas for up to 8 hours per month. In extenuating circumstances (e.g severe

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			aggressive behavior that is responding to interventions but requires increased intensity), an additional 8 hours per month is recommended for coverage
BB	6	**Inclusion of information generated by experts in the field** When conducting a review of any literature base, it is beneficial to consult with experts within the field. This allows for a more thorough evaluation of all relevant evidence. Based on the evidence considered within the current HERC report, it appears that the HERC did not work with or consider the recommendations of experts within the field of behavior analysis. Had the committee done so, the immense body of missing evidence from the report would not be so evident. To correct this oversight, I urge the committee to either amend their report to include additional evidence from experts within the field of behavior analysis or include an addendum to their report with additional evidence generated by a group of experts on behavior-analytic interventions for individuals with an ASD.	See comment #N3. Topic experts were involved in creation of the Warren report, whose decision was to include SSRD, but only if it reported on at least 10 participants, which meets the evidence-based standard recommended by Horner et al. HERC has also appointed three ad hoc experts with knowledge in the areas of ABA and ASD to assist them in their evaluation.

References Provided by Commenters

Commenter	References
F	Houten, R., Axelrod, S., Bailey, J. S., Favell, J. E., Foxx, R. M., Iwata, B. A., & Lovaas, O. I. (1988). The right to effective behavioral treatment. *Journal of Applied Behavior Analysis*, *21*(4), 381-384. Lovaas, O. I. (1987). Behavioral treatment and normal educational and intellectual functioning in young autistic children. *Journal of consulting and clinical psychology*, *55*(1), 3. Eikeseth, S., Smith, T., Jahr, E., & Eldevik, S. (2007). Outcome for children with autism who began intensive behavioral treatment between ages 4 and 7 a comparison controlled study. *Behavior modification*, *31*(3), 264-278.
H	U.S. Department of Health and Human Services (1999). Mental Health: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institute of Mental Health, p.151-174. HERC (2013). Prioritization of health services – a report to the Governer and the 77th Oregon Legislative Assembly. Health Evidence Review Commission.
I, J, K, L	Behavior Analyst Certification Board. *Health Plan Coverage of Applied Behavior Analysis Treatment for Autism Spectrum Disorder*. Florida: BACB, 2012. Web. http://www.bacb.com/Downloadfiles/ABA_Guidelines_for_ASD.pdf Committee on Child Health Financing. "Essential Contractual Language for Medical Necessity in Children." *Pediatrics* 2013;132;398; originally published online July 29, 2013; DOI: 10.1542/peds.2013-1637 http://pediatrics.aappublications.org/content/132/2/398.full.html Donald Baer, Montrose Wolf, and Todd Risley. "Some Still-Current Dimensions of Applied Behavior Analysis." *Journal of Applied Behavior Analysis*. 20.4 (1987): 313-327. Print. Gregory S. Chasson, Gerald E. Harris, and Wendy J. Neely. "Cost Comparison of Early Intensive Behavioral Intervention and Special Education for Children with Autism." *J Child Fam Stud*. (2007) 16:401–413. Print. DOI 10.1007/s10826-006-9094-1 Sigmund Eldevik. "Using individual participant data to extend the evidence base for early intensive behavioral intervention for children with autism." *APBA Reporter* #22 (2010). Print. Eldevik, S., Hastings, R. P., Hughes, J.C.,Jahr, E., Eikeseth, S., & Cross, S. "Using participant data to extend the evidence base for intensive behavioral intervention for children with autism." *American Journal on Intellectual and Developmental Disabilities*, 115, (2010). 381-405. Print. Gina Green. "Single-case Research Methods for Evaluating Treatments for Autism Spectrum Disorders." *The Future of Pennsylvania, Vol 8: Autism in Pennsylvania: What Lies Ahead?* Harrisburg, PA: The Pennsylvania House of Representatives in Pennsylvania, 2008. 69-81. Print. Gina Green. "Early Intensive Behavior Analytic Intervention for Autism Spectrum Disorders." *Behavioral foundations of effective autism treatment*. Eds. E. Mayville and J.Mulick. Cornwall-on-Hudson, NY: Sloan Publishing, 2011. 183-199. Print. John W. Jacobson, James A. Mulick, and Gina Green. "Cost-Benefit Estimates for Early Intensive Behavioral Intervention for Young Children with Autism – General Model and Single State Case." *Behavioral Interventions*, 13 (1998): 201-226. Print. Sanober Motiwala, Shamali Gupta, Meredith Lilly, Wendy Ungar, and Peter Coyte. "The Cost Effectiveness of Expanding Intensive Behavioral Intervention to All Autistic Children in Ontario." *Healthcare Policy*. Vol 1 No 2 (2006): 135-151. Print. **Systematic Reviews of Applied Behavior Analysis provided by several commenters** Julie Brosnan and Olive Healy. "A review of behavioral interventions for the treatment of aggression in individuals with developmental disabilities." *Research in Developmental Disabilities*. 32 (2011) 437–446. Print. Jonathan Campbell. "Efficacy of behavioral interventions for reducing problem behavior in persons with autism: a quantitative synthesis of single-subject

Commenter	References
	research." *Research in Developmental Disabilities* 24 (2003). 128-130. Print. Dennis R. Dixon, Ryan Bergstrom, Marlena N. Smith, and Jonathan Tarbox. "A review of research on procedures for teaching safety skills to persons with developmental disabilities." *Research in Developmental Disabilities*. 31 (2010). 985–994. Print. Sigmund Eldevik, Richard P. Hastings, J. Carl Hughes, Erik Jahr, Svein Eikeseth, and Scott Cross. "Using Participant Data to Extend the Evidence Base for Intensive Behavioral Intervention for Children With Autism." *American Journal on Intellectual and Developmental Disabilities*. 115.5 (2010). 381-405. Print. Sigmund Eldevik, Richard P. Hastings, J. Carl Hughes, Erik Jahr, Svein Eikeseth, andScott Cross. "Meta-Analysis of Early Intensive Behavioral Intervention for Children With Autism." *Journal of Clinical Child & Adolescent Psychology*. 38:3 (2009). 439-450. Print. http://dx.doi.org/10.1080/15374410902851739 Howard Goldstein. "Communication Intervention for Children with Autism: A Review of Treatment Efficacy." *Journal of Autism and Developmental Disorders*. Vol. 32, No. 5, (2002). 373-396. Louis P. Hagopian, Griffin W. Rooker, and Natalie U. Rolider. "Identifying empirically supported treatments for pica in individuals with intellectual disabilities." *Research in Developmental Disabilities*. 32 (2011). 2114–2120. Print. M. Heyvaert, B. Maes, W. Van den Noortgate, S. Kuppens, and P. Onghena. "A multilevel meta-analysis of single-case and small-n research on interventions for reducing challenging behavior in persons with intellectual disabilities." Research in Developmental Disabilities. 33 (2012). 766–780. Print. Heather K. Jennett, and Louis P. Hagopian. "Identifying Empirically Supported Treatments for Phobic Avoidance in Individuals With Intellectual Disabilities." Behavior Therapy. 39 (2008). 151–161. Print. Tiffany Kodak, Cathleen C. Piazza. "Assessment and Treatment of Feeding and Sleeping Disorders in Children Diagnosed with Developmental Disabilities." Child and Adolescent Psychiatric Clinic of North America. In press. Patricia F. Kurtz, Eric W. Boelter, David P. Jarmolowicz, Michelle D. Chin, and Louis P. Hagopian. "An analysis of functional communication training as an empirically supported treatment for problem behavior displayed by individuals with intellectual disabilities." Research in Developmental Disabilities. 32 (2011) 2935–2942. Print. Russell Lang, Mandy Rispoli, Wendy Machalicek, Pamela J. White, Soyeon Kang, Nigel Pierce, Austin Mulloy, Tina Fragale, Mark O'Reilly, Jeff Sigafoos, and Giulio Lancioni. "Treatment of elopement in individuals with developmental disabilities: A systematic review." Research in Developmental Disabilities. 30 (2009) 670–681. Print. Russell Lang, Richard Mahoney, Farah El Zein, Elizabeth Delaune, and Megan Amidon. "Evidence to practice: treatment of anxiety in individuals with autism spectrum disorders." Neuropsychiatric Disease and Treatment. 7 (2011). 27–30. Print. Hsen-Hsing Ma. "The Effectiveness of Intervention on the Behavior of Individuals With Autism: A Meta-Analysis Using Percentage of Data Points Exceeding the Median of Baseline Phase (PEM)." Behavior Modification. Vol. 33 No. 3. (2009). 339-359. Print. National Standards Report: The National Standards Project – Findings and Conclusions. Randolph, Massachusetts: National Autism Center, 2009. Web. http://www.nationalautismcenter.org/pdf/NAC%20Findings%20&%20Conclusions.pdf Mudford, O., Blampied, N., Phillips, K., Harper, D., Foster, M., Church, J., Hunt, M., Prochnow, J., Rose, D., Arnold-Saritepe, A., Peters, H., Lie, C., Jeffrey, K., Messick, E., Sumpter, C., McEwan, J., & Wilczynski, S. Technical review of published research on applied behaviour analysis interventions for people with autism spectrum disorders: Auckland Uniservices Ltd. Wellington, New Zealand: Ministry of Education. (2009) Brian Reichow, and Fred R. Volkmar. "Social Skills Interventions for Individuals with Autism: Evaluation for Evidence-Based Practices within a Best Evidence Synthesis Framework." J Autism Dev Disord. 40 (2010). 149–166. Print. Brian Reichow, Fred R. Volkmar, and Domenic V. Cicchetti. "Development of the Evaluative Method for Evaluating and Determining Evidence-Based Practices in

Commenter	References
	Autism." *J Autism Dev Disord* 38 (2008). 1311–1319. Print. **Evidence-based guidelines from sources on HERC's "trusted sources" list, meeting HERC's definition of "High Quality" evidence.** *Comparative Effectiveness Review # 26: Therapies for Children With Autism Spectrum Disorders – Executive Summary*, Agency for Healthcare Research and Quality, AHRQ Publication No. 11-EHC029-1, April 2011 *Comparative Effectiveness Review # 26: Therapies for Children With Autism Spectrum Disorders*, Agency for Healthcare Research and Quality, AHRQ Publication No. 11-EHC029-EF, April 2011 New Zealand Guidelines Group. *New Zealand Autism Spectrum Disorder Guideline Supplementary Evidence on Applied Behaviour Analysis*. Wellington; 2010. https://www.health.govt.nz/system/files/documents/pages/supplementary_paper_to_nz_asd_guideline_applied_behaviour_analysis_final.pdf New Zealand Guidelines Group. *The effectiveness of applied behaviour analysis interventions for people with autism spectrum disorder. Systematic Review*. Wellington; 2008. Julie Young, Carolyn Corea, James Kimani, and David Mandell. Final Report on Environmental Scan, Autism Spectrum Disorders (ASDs) Services Project. Submitted to Centers for Medicare & Medicaid Services. IMPAQ International, LLC. March 9, 2010 http://www.impaqint.com/files/4-content/1-6-publications/1-6-2-project-reports/finalasdreport.pdf Clinical Practice Guideline Report of the Guideline Recommendations Autism / Pervasive Developmental Disorders Assessment and Intervention for Young Children (Age 0-3 Years). New York State Department of Health Early Intervention Program, 1999 http://www.nyhealth.gov/community/infants_children/early_intervention/disorders/autism/ Margaret A. Maglione, Daphna Gans, Lopamudra Das, Justin Timbie, and Connie Kasari. For the Technical Expert Panel, and HRSA Autism Intervention Research - Behavioral (AIR-B) Network. "Nonmedical Interventions for Children With ASD: Recommended Guidelines and Further Research Needs." Pediatrics. 2012;130;S169. http://pediatrics.aappublications.org/content/130/Supplement_2/S169.full.html Thomas R. Insel, Chair, Interagency Autism Coordinating Committee. Letter from Interagency Autism Coordinating Committee to The Honorable Kathleen Sebelius Secretary of Health and Human Services recommending public and private insurance coverage of early behavioral interventions for children with autism spectrum disorder (ASD). March 25, 2013. Web. http://iacc.hhs.gov/publications/2013/letter_coverage_032513.shtml **Evidence-based guidelines issued by State and Federal Government Agencies and by the National Autism Center.** Thomas R. Insel, Chair, Interagency Autism Coordinating Committee. Interagency Autism Coordinating Committee Member Roster. (2013). Web. http://iacc.hhs.gov/about/iacc_member_roster_2013.pdf Children's Services Evidence-Based Practice Advisory Committee. Interventions for Autism Spectrum Disorders: State of the Evidence. Maine Department of Health and Human Services and Maine Department of Education. October, 2009. http://www.maine.gov/dhhs/ocfs/cbhs/ebpac/asd-report2009.pdf Thompson Foundation for Autism, Missouri Department of Elementary and Secondary Education, Missouri Department of Mental Health, Mercy Children's Hospital, and Missouri Autism Guidelines Initiative. Autism Spectrum Disorders: Guide to Evidence-based Interventions: A 2012 Consensus Publication. Division of Developmental Disabilities of the Missouri Department of Mental Health, 2012. http://www.autismguidelines.dmh.missouri.gov/documents/Interventions.pdf Committee on Educational Interventions for Children with Autism, National Research Council. . Catherine Lord and James P. McGee, Eds. Educating Children with Autism. Washington, DC: National Academy Press, 2001. Print. http://www.nap.edu/catalog/10017.html Committee on Educational Interventions for Children with Autism, National Research Council. . Catherine Lord and James P. McGee, Eds. "Chapter 10: Problem

Commenter	References
	Behaviors." Educating Children with Autism. Washington, DC: National Academy Press, 2001. Print. 115-132. http://www.nap.edu/catalog/10017.html National Institute of Mental Health. Autism Spectrum Disorders Pervasive Developmental Disorders. Bethesda, MD: U.S. Department of Health and Human Services, National Institute of Mental Health. NIH Publication No. 08-5511, 2008. http://www.nimh.nih.gov/health/publications/autism/nimhautismspectrum.pdf Department of Health and Human Services, US Public Health Service. "Chapter 3: Children and Mental Health." Mental Health: Report of the Surgeon General. 1999. 124-194. http://profiles.nlm.nih.gov/ps/access/NNBBHS.pdf Department of Health and Human Services, US Public Health Service. "Chapter 3: Children and Mental Health." Mental Health: Report of the Surgeon General. 1999. 163-164. http://profiles.nlm.nih.gov/ps/access/NNBBHS.pdf **Miscellaneous coverage decisions by or for private health plans, meeting HERC definition of "Medium Quality" evidence.** Dave Jones, Insurance Commissioner. Senate Select Committee on Autism & Related Disorders Informational Hearing on Health Insurance Coverage for Autism Spectrum Disorders (ASD): Current Regulatory Oversight of Behavioral Intervention Therapy. Department of Insurance responses to Panel Questions, Jul 13, 2011; 10:00 AM-12:30 PM. Paul Terdal. Oregon IRO Decisions Overturning Denials of Applied Behavior Analysis. Sep 1, 2012. PacificSource Health Plans. PacificSource Improves Access to Providers of ABA in Treatment of Autism Spectrum Disorder. Feb 14, 2013. Web. **Court orders declaring ABA to be evidence-based and directing state Medicaid agencies to provide coverage, meeting HERC definition of "Medium Quality" evidence** K.G. v. Dudek. Case No. 11-20684-CIV-LENARD / O'SULLIVAN, U.S. District Court for the Southern District of Florida, Nov. 5, 2013, Doc 186. K.G. v. Dudek. Case No. 11-20684-CIV-LENARD / O'SULLIVAN, U.S. District Court for the Southern District of Florida, Nov. 5, 2013, Doc 187. K.G. v. Dudek. Case No. 11-20684-CIV-LENARD / O'SULLIVAN, U.S. District Court for the Southern District of Florida, Mar. 23, 2012. Transcript. Chisholm v. Greenstein. Case 2:97-cv-03274-CJB-ALC, U.S. District Court for the Eastern District of Louisiana, Feb. 21, 2013. Doc 364-1. Chisholm v. Greenstein. Case 2:97-cv-03274-CJB-ALC, U.S. District Court for the Eastern District of Louisiana, May. 21, 2013. Doc 380. Minter v. Dazzo. Case 2:10-cv-15018-SJM-MJH, U.S. District Court for the Eastern District of Michigan, Jan. 16, 2013. Doc 92-2. Hummel v. Ohio Dept. of Job & Family Servs., 164 Ohio App.3d 776, 2005-Ohio-6651. Parents League for Effective Autism Services v. Jones-Kelley. Case 2:08-cv-00421-JLG-NMK, U.S. District Court for the Southern District of Ohio Eastern Division, Jun 30, 2008. Doc 37. Parents League for Effective Autism Services v. Jones-Kelley. Case: 08-3931, U.S. Court of Appeals for the Sixth Circuit, Jul 29, 2009. Doc 00615623768. S.A.H. v State of Washington Department of Social and Health Services. Case No. 24198-0-III, Court of Appeals of Washington, Division 3. Dec 19, 2006. Washington Autism Alliance and Advocacy v. Porter. Case No. 2:12-cv-00742-RAJ, U.S. District Court for the Western District of Washington. Jul 31, 2012. **Court orders declaring ABA to be evidence-based and directing private and government employer health plans to provide coverage, meeting HERC definition of "Medium Quality" evidence** Berge v. United States of America. Case 1:10-cv-00373-RBW, U.S. District Court for the District of Columbia. Jul 27, 2012, Doc. 119. Churchill and Rolando v. CIGNA. Case 2:10-cv-06911-JS, U.S. District Court for the Eastern District of Pennsylvania. Oct 17, 2013, Doc. 139. D.F. and S.F. v. Porter. Case No. 10-2-29400-7 SEA, Superior Court of Washington for King County. Jun 8, 2011. McHenry v PacificSource. Case 3:08-cv-00562-ST, U.S. District Court for the District of Oregon. Jan 5, 2010, Doc. 59; Apr 16, 2010, Doc. 74; Sep 28, 2010, Doc. 118;

Commenter	References
	Aug 30, 2011, Doc. 185. Potter and Boyer v. Blue Cross Blue Shield of Michigan. Case 2:10-cv-14981-SJM-MJH, U.S. District Court for the Eastern District of Michigan Southern Division. Mar 30, 2013, Doc. 125. **Guidelines issued by professional societies and advocacy organizations, meeting HERC definition of "Medium Quality" evidence.** Volkmar F, Cook EH Jr, Pomeroy J, Realmuto G, and Tanguay P. American Academy of Child and Adolescent Psychiatry Working Group on Quality Issues. "Practice Parameters For The Assessment And Treatment Of Children, Adolescents, And Adults With Autism And Other Pervasive Developmental Disorders." J Am Acad Child Adolesc Psychiatry. 1999 Dec;38(12 Suppl):32S-54S. http://www.aacap.org/galleries/PracticeParameters/Autism.pdf American Psychological Association. "Autism Treatment Options." American Psychological Association. American Psychological Association, 2013. Web. http://www.apa.org/topics/autism/treatment.aspx Behavior Analyst Certification Board. Health Plan Coverage of Applied Behavior Analysis Treatment for Autism Spectrum Disorder. Florida: BACB, 2012. Web. http://www.bacb.com/Downloadfiles/ABA_Guidelines_for_ASD.pdf National Standards Report: The National Standards Project. Randolph, Massachusetts: National Autism Center, 2009. Web. http://www.nationalautismcenter.org/pdf/NAC%20NSP%20Report_FIN.pdf Chris Plauche´ Johnson, Scott M. Myers, and the Council on Children With Disabilities. "Identification and Evaluation of Children With Autism Spectrum Disorders." Pediatrics 2007;120;1183-1215. http://pediatrics.aappublications.org/content/120/5/1183.full.pdf+html Scott M. Myers, Chris Plauché Johnson, and the Council on Children With Disabilities. "Management of Children With Autism Spectrum Disorders." Pediatrics 2007;120;1162-1182. http://pediatrics.aappublications.org/cgi/reprint/120/5/1162 **Peer-reviewed individual studies** Cohen, H., Amerine-Dickens, M. and Smith, T. "Early Intensive Behavioral Treatment: Replication of the UCLA Model in a Community Setting." Journal of Developmental Pediatrics, 2006; Vol. 27, No. 2: pp145-155 Fein, D., et al, "Optimal outcome in individuals with a history of autism." Journal of Child Psychology and Psychiatry. 54:2 (2013), pp 195–205 http://onlinelibrary.wiley.com/doi/10.1111/jcpp.12037/pdf Lovaas O. "Behavioral Treatment and Normal Educational and Intellectual Functioning in Young Autistic Children." Journal of Consulting and Clinical Psychology. 1987; Vol. 55, No. 1: pp3-9 McEachin J, et al. "Long-Term Outcome for Children With Autism Who Receive Early Intensive Behavioral Treatment." American Journal on Mental Retardation. 1993; Vol. 97, No. 4: pp 359-372. Rebecca J. Landa and Luther G. Kalb. "Long-term Outcomes of Toddlers With Autism Spectrum Disorders Exposed to Short-term Intervention." Pediatrics. 2012;130;S186. http://pediatrics.aappublications.org/content/130/Supplement_2/S186.full.html Dawson, G. et al, "Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model." Pediatrics. 2010; Vol. 125, No. 1: pp17-23 . http://pediatrics.aappublications.org/content/125/1/e17.full.pdf+html Brian Reichow, "Overview of Meta-Analyses on Early Intensive Behavioral Intervention for Young Children with Autism Spectrum Disorders." J Autism Dev Disord (2012) 42:512–520. Brian Reichow and Fred R. Volkmar, "Social Skills Interventions for Individuals with Autism: Evaluation for Evidence-Based Practices within a Best Evidence Synthesis Framework." J Autism Dev Disord (2010) 40:149–166.
M	AAP Committee on Child Health Financing (2013). Essential Contractual Language for Medical Necessityin Children. *Pediatrics,* 132, 398-401. DOI:

Commenter	References
	10.1542/peds.2013-1637 Bellini, S., Peters, J.K., Benner, L., & Hopf, A. (2007). A meta-analysis of school-based social skills interventions for children with autism spectrum disorders. *Remedial and Special Education*, 28, 153-162. Brosnan, J., & Healy, O. (2011). A review of behavioral interventions for the treatment of aggression in individuals with developmental disabilities. *Research in Developmental Disabilities*. 32, 437–446. Hanley, G., Iwata, B.A., & McCord, B.E. (2003). Functional analysis of problem behavior: A review. *Journal of Applied Behavior Analysis*, 36, 147-185. Iwata, B.A., Pace, G.M., et al. (1994). The functions of self-injurious behavior: An experimental epidemiological analysis. *Journal of Applied Behavior Analysis*, 27, 215-240. Lang, R., Regester, A., Lauderdale, S., Ashbaugh, K., & Haring, A. (2010). Treatment of anxiety in autismspectrum disorders using cognitive behaviour therapy: a systematic review. *Developmental Neurorehabilitation*, 13, 53–63. Reichow, B. & Volkmar, F.R. (2010). Social Skills Interventions for Individuals with Autism: Evaluation for Evidence-Based Practices within a Best Evidence Synthesis Framework. *Journal of Autism and Developmental Disorders.* 40, 149-166. SAMHSA (2007). Center for Substance Abuse Treatment. *Understanding Evidence-Based Practices for Co-Occurring Disorders. COCE Overview Paper 5.* DHHS Publication No. (SMA) 07-4278. Rockville,MD: Substance Abuse and Mental Health Services Administration, and Center for Mental Health Services, 2007. **Specific References of Within Subject Experiments on Applied Behavior Analysis with Older Children:** Baer, D. M., Peterson, R.F., & Sherman, J.A. (1967). The development of imitation by reinforcing behavioral similarity to a model. *Journal of the Experimental Analysis of Behavior*, 10, 405-416. Baer, D.M. & Guess, D. (1971). Receptive training of adjectival inflections in mental retardates. *Journal of Applied Behavior Analysis*, 4, 129-139. Baer, D.M. & Guess, D. (1973). Teaching productive noun suffixes to severely retarded children. *AmericanJournal of Mental Deficiency*, **77** (5), 498-505. Barbetta, P.M., Heron, T.E., & Heward, W.L., (1993). Effects of active student response during errorcorrection on the acquisition, maintenance, and generalization of sight words by students with developmental disabilities. *Journal of Applied Behavior Analysis, 26,* 111-120. Barbetta, P.M., Heward, W.L., & Bradley, D.M. (1993). Relative effects of whole-word and phonetic prompt error correction on the acquisition and maintenance of sight words by students with developmental disabilities. *Journal of Applied Behavior Analysis. 26,* 99-111. Belchic, J.K., & Harris, S.L. (1994). The use of multiple peer exemplars to enhance the generalization of play skills to the siblings of children with autism. *Child and Family Behavior Therapy, 16,*1-25. Bellini, S., & Akullian, J. (2007). A Meta-Analysis of Video Modeling and Video Self-Modeling Interventions for Children and Adolescents with Autism spectrum disorders. *Exceptional Children*, 73, 261-284. Bellini, S., Peters, J.K., Benner, L., & Hopf, A. (2007). A meta-analysis of school-based social skills interventions for children with autism spectrum disorders. *Remedial and Special Education*, 28, 153- 162. Bernard-Opitz, V., Sriram, N., & Nakhoda-Sapuan, S. (2001). Enhancing social problem solving in children with autism and normal children through computer-assisted instruction. *Journal of Autism& Developmental Disorders*, 31, 377-384. Bibby, P., Eikeseth, S., Martin, N.T., Mudford, O.C., & Reeves, D. (2001). Progress and outcomes for children with autism receiving parent-managed intensive interventions. *Research in Developmental Disabilities*. 22, 425-447. Billingsly, F.F., & Neel, R.S. (1985). Competing behaviors and their effects on skill generalization and maintenance. *Analysis and Intervention in Developmental Disabilities, 5*, 357-372.

Commenter	References
	Blew, P.A., Schwartz, I.S., & Luce, S.C. (1985). Teaching functional community skills to autistic children using nonhandicapped peer tutors. *Journal of Applied Behavior Analysis. 18,* 337-342. Brown, F., Holvoet, J., Guess, D., & Mulligan, M. (1980). Individualized curriculum sequencing model (III): Small group instruction. *Journal of the Association for the Severely Handicapped*, 5, 352-367. Buggey, T., Toombs, K., Gardener, P., Cervetti, M. (2000). Training responding behaviors in students with autism: Using videotaped self-modeling. *Journal of Positive Behavior Interventions, 1,* 205-214. Burgess, R. L., Burgess, J. M., & Esveldt, K. C. (1970). An analysis of generalized imitation. *Journal of Applied Behavior Analysis*, 3, 39-46. Camarata, S. (1993). The application of naturalistic conversation training to speech production in children with speech disabilities. *Journal of Applied Behavior Analysis, 26.* 173-182. Carr, E. G., Newsome, C. D., & Binkoff, J. A. (1980). Escape as a factor in the aggressive behavior of two retarded children. *Journal of Applied Behavior Analysis, 13,* 101-117. Casey, L.O. (1978). Development of communicative behavior in autistic children: a parent program using manual signs. *Journal of autism & childhood schizophrenia*. 8, 45-59. Celiberti, D.A., & Harris, S.L. (1993). Behavioral intervention for siblings of children with autism: A focus on skills to enhance play. *Behavior Therapy,* 24(4). 573-599. Charlop, M.H. (1983). The effects of echolalia on acquisition and generalization of receptive labeling in autistic children. *Journal of Applied Behavior Analysis. 16,* 111-127. Charlop, M.H., & Milstein, J.P. (1989). Teaching autistic children conversational speech using video modeling. *Journal of Applied Behavior Analysis. 22,* 275-286. Charlop, M.H., & Trasowech, J.E., (1991). Increasing autistic children's daily spontaneous speech. *Journal of Applied Behavior Analysis. 24,* 747-762. Charlop, M.H., & Walsh, M.E. (1986). Increasing autistic children's spontaneous verbalizations of affection: An assessment of time delay and peer modelling procedures. *Journal of Applied Behavior Analysis, 19,* 307-314. Charlop, M.H., Kurtz, P.F., & Casey, F.G. (1990). Using aberrant behaviors as reinforcers for autistic children. *Journal of Applied Behavior Analysis. 23,* 163-182. Charlop, M.H., Kurtz, P.F., & Milstein, J.P. (1992). Too much reinforcement, too little behavior:Assessing task interspersal procedures in conjunction with different reinforcement schedules with autistic children. *Journal of Applied Behavior Analysis, 25,* 795-808. Charlop, M.H., Schreibman, L., & Tryon, A.S. (1983). Learning through observation: The effects of peer modeling on acquisition and generalization in autistic children. *Journal of Abnormal Child Psychology,* 11, 355-366. Charlop, M.H., Schreibman, L., & Thibodeau, M.G. (1985). Increasing spontaneous verbal responding in autistic children using a time delay procedure. *Journal of Applied Behavior Analysis, 18,* 155-166. Christy, P.R. (1975). Does use of tangible rewards with individual children affect peer observers? *Journal of Applied Behavior Analysis. 8,* 187-196. Clark, H. B. & Sherman, J. A. (1975). Teaching generative use of sentence answers to three forms of questions. *Journal of Applied Behavior Analysis,* **8**, 321-330. Cook, C., & Adams, H.F. (1966). Modification of verbal behavior in speech deficient children. *Behaviour Research and Therapy, 4,* 265-271. Cowdery, G. E., Iwata, B. A., & Pace, G. M. (1990). Effects and side effects of DRO as treatment for self-injurious behavior. *Journal of Applied Behavior Analysis, 23,* 497-506. Craighead, W.E., O'Leary, K.D., & Allen, J.S. (1973). Teaching and generalization of instruction following in an "autistic" child. *Journal of Behavior Therapy and Experimental Psychiatry, 4,* 171-176.

Commenter	References
	Crockett, J.L., Fleming, R.K., Doepke, K.J., & Stevens, J.S. (2007). Parent training: Acquisition and generalization of discrete trials teaching skills with parents of children with autism. *Research in Developmental Disabilities. 28, 23-36.* Curl, R.M., Rowbury, T.G., & Baer, D.M. (1985). The facilitation of children's social interaction by a picture-cue training program. *Child and Family Behavior Therapy. 7,* 11-39. Davison, G.C. (1964). A social learning therapy programme with an autistic child. *Behavior Research and Therapy, 2,* 149-159. Delano, M.E. (2007). Improving written language performance of adolescents with Asperger syndrome. *Journal of Applied Behavior Analysis,* 40, 345-351. Dunlap, G. (1984). The influence of task variation and maintenance tasks on the learning and affect of autistic children. *Journal of Experimental Child Psychology,* 37, 41-46. Dunlap, G., Koegel, R. L., & Kern, L. (1984). Continuity of treatment: Toilet training in multiple community settings. *Journal of the Association for Persons with Severe Handicaps, 9*, 134-142. Dunlap, G., & Johnson, J., (1985). Increasing the independent responding of autistic children with unpredictable supervision. *Journal of Applied Behavior Analysis. 18,* 227-236. Dunlap, G., & Koegel, R.L. (1980). Motivating autistic children through stimulus variation. *Journal of Applied Behavior Analysis,* 13*,* 619-627. Dunlap, G., Dyer, K., & Koegel, R.L. (1983). Autistic self-stimulation and intertrial interval duration. *American Journal of Mental Deficiency*, 88, 194-202. Dunlap, G., Koegel, R.L., Johnson, J., & O'Neill, R.E. (1986). Maintaining performance of autistic clients in community settings with delayed contingencies. *Journal of Applied Behavior Analysis. 20,* 185-192. Durand, V. M., & Carr, E. G. (1987). Social influences on "self-stimulatory" behavior: Analysis and treatment application. *Journal of Applied Behavior Analysis, 20,* 119-132. Durand, V. M., & Crimmins, D. B. (1987). Assessment and treatment of psychotic speech in an autistic child. *Journal of Autism and Developmental Disorders, 17*, 17-28. Dyer, K. I. (1987). The competition of autistic stereotyped behavior with usual and specially assessed reinforcers. *Research in Developmental Disabilities, 8*, 607-626. Dyer, K., Christian, W.P., & Luce, S.C. (1982). The role of response delay in improving the discrimination performance of autistic children. *Journal of Applied Behavior Analysis,* 15, 231-240. Dyer, K., Dunlap, G., & Winterling, V. (1990). Effects of choice making on the serious problem behaviors of students with severe handicaps. *Journal of Applied Behavior Analysis, 23,* 515-524. Dyer, K., Schwartz, I.S., & Luce, S.C. (1984). A supervision program for increasing functional activities for severely handicapped students in a residential setting. *Journal of Applied Behavior Analysis*, 17, 249-260. Egel, A. L., Richman, G. S., & Koegel, R. L. (1981). Normal peer models and autistic children's learning. *Journal of Applied Behavior Analysis,* 14, 3-12. Egel, A.L., (1981). Reinforcer variation: Implications for motivating developmentally disabled children. *Journal of Applied Behavior Analysis. 14, 345-350.* Eikeseth, S., & Smith, T. (1992). The development of functional and equivalence classes in high functioning autistic children: The role of naming. *Journal of the Experimental Analysis of Behavior*, *58*, 123-133. Favell, J.E., Favell, J.E., & McGimsey, J.F. (1978). Relative effectiveness and efficiency of group vs. Individual training of severely retarded persons. *American Journal of Mental Deficiency*, 83, 104- 109. Fineman, K.R. (1968). Visual-color reinforcement in establishment of speech by an autistic child. *Perceptual and Motor Skills, 26,* 761-762.

Commenter	References
	Foss, D. (1968). Learning and discovery in the acquisition of structured material. Effects of number of items and their sequence. *Journal of Experimental Psychology,* **77**, 341-344 Foxx, R.M. & Azrin, N.H. (1973). The elimination of autistic self-stimulatory behavior by overcorrection. *Journal of Applied Behavior Analysis.* 6, 1-14. Foxx, R.M. & Livesay, J. (1984). Maintenance of response suppression following overcorrection: A 10-year retrospective examination of eight cases. *Analysis and Intervention in Developmental Disabilities, 4*, 65-80. Frea, W.D., & Hepburn, S.L. (1999). Teaching parents of children with autism to perform functional assessments to plan interventions for extremely disruptive behaviors. *Journal of Positive Behavior Interventions,* 1, 112-116. Garcia, E. E. (1976). The development and generalization of delayed imitation. *Journal of Applied behavior Analysis*, 9, 499. Garcia, E.E. (1974). The training and generalization of a conversational speech form in nonverbal retardates. *Journal of Applied Behavior Analysis.* 7, 137-151. Garcia, E.E., Baer, D.M., & Firestone, I. (1971). The development of generalized imitation within topographically determined boundaries. *Journal of Applied Behavior Analysis.* 4, 101-113. Garcia, E.E., Guess, D., & Byrnes, J. (1973). Development of syntax in a retarded girl using procedures of imitation, reinforcement, and modeling. *Journal of Applied Behavior Analysis.* 6, 299-311. Gaylord-Ross, R.J., Haring, T.G., Breen, C., & Pitts-Conway, V. (1984). The training and generalization of social interaction skills with autistic youth. *Journal of Applied Behavior Analysis*, 17, 229-248. Gena, A., Krantz, P., McClannahan, L.E., & Poulson, C.L. (1996). Training and generalization of affective behavior displayed by youth with autism. *Journal of Applied Behavior Analysis, 29,* 291-304. Goldstein, H. (1983). Recombinative generalization: Relationships between environmental conditions and the linguistic repertoires of language learners. *Analysis and Intervention in Developmental Disabilities*, **3**, 279-293. Goldstein, H., & Mousetis, L. (1989). Generalized language learning by children with severe mental retardation: Effects of peers' expressive modeling expressive modeling. *Journal of Applied Behavior Analysis,* ***22****,* 245-259. Goldstein, H., Angelo, D., & Mousetis, L. (1987). Acquisition and extension of syntactic repertoires by severely mentally retarded youth. *Research in Developmental Disabilities*, **8**, 549-574. Guess, D. (1969). A functional analysis of receptive language and productive speech: Acquisition of the plural morpheme. Journal *of Applied Behavior Analysis.* 2, 55-64. Guess, D., & Baer, D.M., (1973). An analysis of individual differences in generalization between receptive and productive language in retarded children. *Journal of Applied Behavior Analysis.* 6, 311-331. Guess, D., Sailor, W., Rutherford, G., & Baer, D.M. (1968). An experimental analysis of linguistic development: The productive use of the plural morpheme. *Journal of Applied Behavior Analysis.* 1, 292-307. Hagopian, L.P., Kuhn, D.E. & Strother, G.E. (2009). Targeting social skills deficits in an adolescent with pervasive developmental disorder. *Journal of Applied Behavior Analysis*, 42, 907-911. Hall, R.V., & Broden, M. (1967). Behavior changes in brain-injured children through social reinforcement. *Journal of Experimental Child Psychology. 5,* 463-479. Halle, J.W. (1987). Teaching language in the natural environment: An analysis of spontaneity. *Journal of The Association for Persons with Severe Handicaps, 12*, 28-37. Halle, J.W., Baer, D.M., & Spradlin, J.E. (1981). Teacher's generalized use of delay as a stimulus control procedure to increase language use in handicapped

Commenter	References
	children. *Journal of Applied Behavior Analysis, 14,* 389-409. Halle, J.W., Marshall, A.M., & Spradlin, J.E. (1979). Time delay: A technique to increase language use and facilitate generalization in retarded children. *Journal of Applied Behavior Analysis,* 12*,* 431-439. Handleman, J.S. (1979). Generalization by autistic-type children of verbal responses across settings. *Journal of Applied Behavior Analysis*, 12, 273-282. Haring, T.G. (1985). Teaching between-class generalization of toy play behavior to handicapped children. *Journal of Applied Behavior Analysis. 18,* 127-140. Haring, T.G., & Breen, C.G. (1992). A peer-mediated social network intervention to enhance the social integration of persons with moderate and severe disabilities. *Journal of Applied Behavior Analysis*, 25, 319-333. Haring, T.G., Roger, B., Lee, M., Breen, C., Gaylord-Ross, R. (1986). Teaching social language to moderately handicapped students. *Journal of Applied Behavior Analysis, 19,* 159-171. Harris, S.L. (1986). Parents as teachers: A four to seven year follow up of parents of children with autism. *Child & Family Behavior Therapy, 8*, 39-47. Harris, S.L. & Handleman, J.S. (1980). Programming for generalization: Educating autistic children and their parents. *Education and Treatment of Children.* 3, 51-63. Harris, S. L., Handleman, J. S., & Alessandri, M. (1990). Teaching youths with autism to offer assistance. *Journal of Applied Behavior Analysis*, 23, 297-305. Harris, S.L., Wolchik, S.A., & Weitz, S. (1981). The acquisition of language skills by autistic children: can parents do the job? *Journal of autism & developmental disorders*. 11, 373-384. Hewitt, F.M. (1965). Teaching speech to an autistic child through operant conditioning. *American Journal of Orthopsychiatry*, 35, 927-936. Hintgen, J.N., & Coulter, S.K. (1967). Auditory control of operant behavior in mute autistic children. *Perceptual and Motor Skills, 25,* 561-565. Horner, R. H. Dunlap, G. & Koegel, R. L., (Eds.). (1988). *Generalization and maintenance: Life-style changes in applied settings.* Baltimore, MD: Brooks. Hunt, P., Alwell, M., & Goetz, L. (1988). Acquisition of conversational skills and the reduction of inappropriate social interaction behaviors. *Journal of the Association for Persons with Severe Handicaps, 13,* 20-27. Ingenmey, R., & Van Houten, R. (1991). Using time delay to promote spontaneous speech in an autistic child. *Journal of Applied Behavior Analysis, 24,* 591-596. Iwata, B. A., Dorsey, M. F., Slifer, K. J., Bauman, K. E., & Richman, G. S. (1982). Toward a functional analysis of self-injury. *Analysis and Intervention in Developmental Disabilities, 2,* 3-20. Iwata, B. A., Pace, G. M., Cowdery, G. E., Kalsher, M. J., & Cataldo, M. F. (1990). Experimental analysis and extinction of self-injurious escape behavior. *Journal of Applied Behavior Analysis, 23,* 11-27. Johnson, S. C., Larsson, E. V., & Luce, S. C. (1989, November). Follow-up measures of program effectiveness: Ten years of behavioral programming at the May Institute. In E. V. Larsson (Chair), *The sustained evaluation and development of a comprehensive program of services for children with autism.* Symposium conducted at the twenty-third annual convention of the Association for Advancement of Behavior Therapy, Washington, DC. Jordan, J., Singh, N.N., & Repp, A.C. (1989). An evaluation of gentle teaching and visual screening in the reduction of stereotypy. *Journal of Applied Behavior Analysis. 22,* 9-22. Kamps, D., Greenwood, C. R., & Leonard, B. (1991). Ecobehavioral assessment in classrooms serving children with autism and developmental disabilities. In R. J., Prinz (Ed.), Advances in behavioral assessment of children and families (pp. 203-237). New York: Jessica Kingsley. Kamps, D., Potucek, J., Dugan, E., Kravits, T., Gonzalez-Lopez, A., Garcia, J., Carnazzo, K., Morrison, L.,& Garrison-Kane, L. (2002). Peer training to facilitate social interaction for students with autism. *Exceptional Children, 68,* 173-187. Kamps, D., Wills, H. P., Greenwood, C. R., Thorne, S., Lazo, J. F., Crockett, J. L., Akers, J. M., & Swaggart, B. L. (2003). A descriptive study of curriculum influences on

Commenter	References
	the early reading fluency of students with academic and behavioral risks. *Journal of Emotional and Behavioral Disorders, 11*(4), 211-224. Kamps, D.M., Barbetta, P.M., Leonard, B.R., & Delquadri, J., (1994). Classwide peer tutoring: An integration strategy to improve reading skills and promote peer interactions among students with autism and general education peers. *Journal of Applied Behavior Analysis, 27,* 49-62. Kamps, D.M., Leonard, B.R., Vernon, S., Dugan, E.P., Delquadri, J.C., Gershon, B., Wade, L., & Folk, L., (1992). Teaching social skills to students with autism to increase peer interactions in an integrated first-grade classroom. *Journal of Applied Behavior Analysis. 25,* 281-288. Karlan, G. R., Brenn-White, B., Lentz, A., Hodur, P., Egger, D., & Frankoff, D. (1982). Establishing generalized productive verb-noun phrase usage in a manual language system with moderately handicapped children. *Journal of Speech and Hearing Disorders,* **47**, 31-42. Kern, L., Childs, K. E., Dunlap, G., Clarke, S., & Falk, G. D. (1994). Using assessment-based curricular intervention to improve the classroom behavior of a student with emotional and behavioral challenges. *Journal of Applied Behavior Analysis,* 27, 7-19. Koegel, R. L., & Covert, A. (1972). The relationship of self-stimulation to learning in autistic children. *Journal of Applied Behavior Analysis, 5*, 381-388. Koegel, R. L., & Schreibman, L. (1977). Teaching autistic children to respond to simultaneous multiple cues. *Journal of Experimental Child Psychology, 24,* 299-311. Koegel, R. L., Firestone, P. B., Kramme, K. W., & Dunlap, G. (1974). Increasing spontaneous play by suppressing self-stimulation in autistic children. *Journal of Applied Behavior Analysis, 7,* 521-528. Koegel, R. L., Schreibman, L., Britten, K. R., Burke, J. C., & O'Neill, R. E. (1982). A comparison of parent training to direct child treatment. In R. L. Koegel, A. Rincover, & A. L. Egel (Eds.), *Educating and understanding autistic children.* San Diego, CA: College-Hill Press. Koegel, R. L., Schreibman, L., Johnson, J., O'Neill, R. E., & Dunlap, G. (1984). Collateral effects of parent training on families with autistic children. In R. F. Dangel & R. A. Polster (Eds.), *Parent training: Foundations of research and practice.* New York: Guilford. Koegel, R.L, & Rincover, A., (1976). Some detrimental effects of using extra stimuli to guide learning in normal and autistic children. *Journal of Abnormal Child Psychology*, 4, 59-71. Koegel, R.L, & Rincover, A., (1977). Research on the difference between generalization and maintenance in extra-therapy responding. *Journal of Applied Behavior Analysis*, 10, 1-12. Koegel, R.L, Dunlap, G., & Dyer, K. (1980). Intertrial interval duration and learning in autistic children. *Journal of Applied Behavior Analysis,* 13, 91-99. Koegel, R.L, Dunlap, Richman, G.S., & Dyer, K. (1981). The use of specific orienting cures for teaching discrimination tasks. *Analysis and Intervention in Developmental Disabilities*, 1, 187-198. Koegel, R.L, Russo, D.C., & Rincover, A., (1977). Assessing and training teachers in the generalized use of behavior modification with autistic children. *Journal of Applied Behavior Analysis*, 10, 197-205. Koegel, R.L., & Egel, A.L. (1979). Motivating autistic children. *Journal of Abnormal Psychology*, 88, 418- 425. Koegel, R.L., & Frea, W.D. (1993). Treatment of social behavior in autism through the modification of pivotal social skills. *Journal of Applied Behavior Analysis, 26,* 369-378. Koegel, R.L., & Rincover, A. (1974). Treatment of psychotic children in a classroom environment: I. Learning in a large group. *Journal of Applied Behavior Analysis, 7,* 45-59. Koegel, R.L., & Wilhelm, H. (1973). Selective responding to the components of multiple visual cues by autistic children. *Journal of Experimental Child Psychology.* 15, 442-453. Koegel, R.L., Bimbela, A., & Schreibman, L. (1996). Collateral effects of parent training on family interactions. *Journal of Autism and Developmental Disorders*, 26, 347-359.

Commenter	References
	Koegel, R.L., Dyer, K, & Bell, L.K. (1986). The influence of child-preferred activities on autistic children's social behavior. *Journal of Applied Behavior Analysis. 20,* 243-252. Koegel, R.L., Glahn, T.J. & Nieminen, G.S. (1978). Generalization of parent-training results. *Journal of Applied Behavior Analysis*, *11*, 95-109. Koegel, R.L., O'Dell, M.C., & Koegel, L.K. (1987). A natural language paradigm for teaching autistic children by reinforcing attempts. *Journal of Autism and Developmental Disorders, 17,* 187-199. Krantz, P.J., & McClannahan, L.E. (1993). Teaching children with autism to initiate to peers: Effects of a script-fading procedure. *Journal of Applied Behavior Analysis, 26,* 121-132. Krantz, P.J., & McClannahan, L.E. (1998). Social interaction skills for children with autism: A scriptfading procedure for beginning readers. *Journal of Applied Behavior Analysis*, 31, 191-202. Krantz, P.J., MacDuff, M.T., & McClannahan, L.E. (1993). Programming participation in family activities for children with autism: Parents' use of photographic activity schedules. *Journal of Applied Behavior Analysis*, 26, 137-138. Krantz, P.J., Zalenski, S., Hall, L.J., Fenske, E.C., & McClannahan, L.E. (1981). Teaching complex language to autistic children. *Analysis and Intervention in Developmental Disabilities.* 1, 259-297. Kravits, T., Kamps, D., Carnazzo, K., & Potucek, J. (2002). Increasing communication skills for an elementary-aged student with autism using the Picture Exchange Communication System. *Journal of Autism and Developmental Disabilities, 32*, 225-230. Kuhn, D.E., Hardesty, S.L. & Sweeney, N.M. (2009). Assessment and treatment of excessive straightening and destructive behavior in an adolescent diagnosed with autism. *Journal of Applied Behavior Analysis,* 42, 355-360. Larsson, D. G., & Larsson, E. V. (1983). Manipulating peer presence to program the generalization of verbal compliance from one-to-one to group instruction. *Education and Treatment of Children*, 6, 109-122. Leaf, J.B., Oppenheim-Leaf, M.L., Call, N.A., Sheldon, J.B., Sherman, J.A., Taubman, M., McEachin, J., Dayharsh, J., & Leaf, R. (2012). Comparing the teaching interaction procedure to social stories for people with autism. *Journal of Applied Behavior Analysis,* 45, 281-298. Lovaas, O. I., & Taubman, M. T. (1981). Language training and some mechanisms of social and internal control. *Journal of Analysis and Intervention in Developmental Disabilities*, 4, 363-372. Lovaas, O.I. (1968). Some studies on the treatment of childhood schizophrenia. *Research in Psychotherapy.* 3, 103-121. Lovaas, O.I. (1968). A program for the establishment of speech in psychotic children. In H.N. Sloane, & B.D. MacAulay (Eds.). *Operant procedures in remedial speech and language training.* Boston: Houghton, Mifflin. Lovaas, O.I., & Schreibman, L. (1971). Stimulus overselectivity of autistic children in a two-stimulus situation. *Behaviour Research and Therapy, 9,* 305-310. Lovaas, O.I., & Simmons, J.Q. (1969). Manipulation of self-destruction in three retarded children. *Journal of Applied Behavior Analysis,* 2, 143-157. Lovaas, O.I., Berberich, J.P., Perloff, B.F., & Schaeffer, B. (1966). Acquisition of imitative speech in schizophrenic children. *Science*, 151, 705-707. Lovaas, O.I., Freitag, G., Gold, V.J., & Kassorla, I.C. (1965). Experimental studies in childhood schizophrenia: Analysis of self-destructive behavior. *Journal of Experimental Child Psychology*, 2, 67-84. Lovaas, O.I., Freitag, G., Kinder, M.I., Rubenstein, B.D., Schaeffer, B., & Simmons, J.W. (1966). Establishment of social reinforcers in two schizophrenic children on the basis of food. *Journal of Experimental Child Psychology.* 4, 109-125. Lovaas, O.I., Freitas, L., Nelson, K., & Whalen, C. (1967). The establishment of imitation and its use for the development of complex behavior in schizophrenic children. *Behavior Research and Therapy,* 5, 171-181.

Commenter	References
	Lovaas, O.I., Litrownik, A., & Mann, R. (1971). Response latencies to auditory stimuli in autistic children engaged in self-stimulatory behavior. *Behavior Research and Therapy,* 9, 39-49. Lovaas, O.I., Schreibman, L., Koegel, R.L., & Rehm, R. (1971). Selective responding by autistic children to multiple sensory input. *Journal of Abnormal Psychology, 77,* 211-222. Luce, S. C., Christian, W. P., Anderson, S. R., Troy, P. J., & Larsson, E. V., (1991). Development of a continuum of services for children and adults with autism and other severe behavior disorders. *Research in Developmental Disabilities*, *13*, 9-25. Lutzker, J. R., & Sherman, J. A. (1974). Producing generative sentence usage by imitation and reinforcement procedures. *Journal of Applied Behavior Analysis*, **7** (3), 447-460. MacDuff, G.S., Krantz, P.J., & McClannahan, L.E. (1993). Teaching children with autism to use photographic activity schedules: Maintenance and generalization of complex response chains. *Journal of Applied Behavior Analysis*, 26, 89-97. Mace, F.C., Hock, M.L., Lalli, J.S., West, B. J., Belfiore, P., Pinter, E., & Brown, D.K. (1988). Behavioral momentum in the treatment of noncompliance. *Journal of Applied Behavior Analysis. 21,* 123-142. Mason, S.A., & Iwata, B. A. (1990). Artifactual effects of sensory-integrative therapy on self-injurious behavior. *Journal of Applied Behavior Analysis. 23,* 361-370. McClannahan, L.E., Krantz, P.J., & McGhee, G.G. (1982). Parents as therapists for autistic children: A model for effective parent training. *Analysis and Intervention in Developmental Disabilities.* 2, 223- 252. McEntee, J.E. & Saunders, R.R. (1997). A response-restriction analysis of stereotypy in adolescents with mental retardation: Implications for applied behavior analysis. *Journal of Applied Behavior Analysis*, 30, 485-506. McGee, G.G., Krantz, P.J., & McClannahan, L.E. (1985). The facilitative effects of incidental teaching on preposition use by autistic children. *Journal of Applied Behavior Analysis. 18,* 17-32. McGee, G.G., Krantz, P.J., Mason, D., & McClannahan, L.E. (1983). A modified incidental-teaching procedure for autistic youth: Acquisition and generalization of receptive object labels. *Journal of Applied Behavior Analysis. 16,* 329-338. McMorrow, M. J., Foxx, R. M., Faw, G. D., & Bittle, R. G. (1986). Cues-pause-point language training: Teaching echolalics functional use of their verbal labeling repertoires. *Journal of Applied Behavior Analysis, 20*, 11-22. McReynolds, L.V. (1969). Application of time out from positive reinforcement for increasing the efficiency of speech training. *Journal of Applied Behavior Analysis. 2,* 199-205. Metz, J.R. (1965). Conditioning generalized imitation in autistic children. *Journal of Experimental Child Psychology, 2,* 389-399. Miller, N. & Neuringer, A. (2000). Reinforcing variability in adolescents with autism. *Journal of Applied Behavior Analysis,* 33, 151-165. Mineo, B. A., & Goldstein, H. (1990). Generalized learning of receptive and expressive action-object responses by language-delayed preschoolers. *Journal Speech and Hearing Disorders*, **55**, 665-678. Mithaug, D.E., & Wolfe, M.S., (1976). Employing task arrangements and verbal contingencies to promote verbalizations between retarded children. *Journal of Applied Behavior Analysis*, 9, 301-314. Moes, D.R., & Frea, W.D. (2002). Contextualized behavioral support in early intervention for children with autism and their families. Journal of Autism and Developmental Disorders, 32, 519–533. Morrison, L., Kamps, D., Garcia, J., & Parker, D. (2001). Peer mediation and monitoring strategies to improve initiations and social skills for students with autism. *Journal of Positive Behavior Interventions, 3,* 237-250.

Commenter	References
	Murphy, C., & Barnes-Holmes, D. (2010). Establishing five derived mands in three adolescent boys with autism. *Journal of Applied Behavior Analysis*, 43, 537-541. Murphy, H.A., Hutchinson, J.M., & Bailey, J.S., (1983). Behavioral school psychology goes outdoors: The effect of organized games on playground aggression. *Journal of Applied Behavior Analysis*, 16, 29-36. Neef, N.A., Shafer, M.S., Egel, Andrew L., Cataldo, M.F., & Parrish, J.M. (1983). The class specific effect of compliance training with "do" and "don't" requests: Analogue analysis and classroom application. *Journal of Applied Behavior Analysis. 16,* 81-100. Neef, N.A., Walters, J., & Egel, A. L. (1984). Establishing generative yes/no responses in developmentally disabled children. *Journal of Applied Behavior Analysis. 17,* 453-460. Nelson R., Gibson, F., & Cutting, D.S. (1973). Video taped modeling: The development of three appropriate social responses in a mildly retarded child. *Mental Retardation.* 11, 24-28. Nikopoulos, C.K. & Keenan, M. (2003). Promoting social initiation in children with autism using video modeling. *Behavioral Interventions*, 18, 87-108. Nordquist, V.M., & Wahler, R.G. (1973). Naturalistic treatment of an autistic child. *Journal of Applied Behavior Analysis*, 6, 79-87. O'Dell, S.L., Blackwell, L.J., Larcen, S.W. & Hogan, J.L. (1977). Competency based training for severely behaviorally handicapped children and their parents. *Journal of Autism and Childhood Schizophrenia*, *7*, 231-242. O'Connor, R.D. (1969). Modification of social withdrawal through symbolic modeling. *Journal of Applied Behavior Analysis. 2,* 15-22. Pace, G.M., Ivancic, M.T., Edwards, G.L., Iwata, B.A., & Page, T.J. (1985). Assessment of stimulus preference and reinforcer value with profoundly retarded individuals. *Journal of Applied Behavior Analysis*, 18, 249-255. Piazza, C.C., & Fisher, W., (1991). A faded bedtime with response cost protocol for treatment of multiple sleep problems in children. *Journal of Applied Behavior Analysis. 24*, 129-140. Pierce, K., & Schreibman, L. (1997). Multiple peer use of pivotal response training to increase social behaviors of classmates with autism: Results from trained and untrained peers. *Journal of Applied Behavior Analysis*, 30, 157-160. Pierce, K., & Schreibman, L., (1995). Increasing complex social behaviors in children with autism: Effects of peer-implemented pivotal response training. *Journal of Applied Behavior Analysis, 28.* 285-296. Pierce, K.L., & Schreibman, L. (1994). Teaching daily living skills to children with autism in unsupervised settings through pictorial self-management. *Journal of Applied Behavior Analysis*, 27, 471-481. Powers, L.E., Singer, G.H.S., Stevens, T. & Sowers, J. (1992). Behavioral parent training in home and community generalization settings. *Education and Training in Mental Retardation*, 13-27. Rabb, E., & Hewitt, F.M. (1967). Development of appropriate classroom behaviors in a severely disturbed group of institutionalized children with a behavior modification model. *American Journal of Orthopsychiatry,* 37, 313-314. Rekers, G.A., & Lovaas, O.I. (1974). Behavioral treatment of deviant sex-role behaviors in a male child. *Journal of Applied Behavior Analysis. 7,* 173-190. Repp, A. C., & Deitz, S. M. (1974). Reducing aggressive and self-injurious behavior of institutionalized retarded children through reinforcement of other behaviors. *Journal of Applied Behavior Analysis, 7,* 313-326. Repp, A.C., Karsh, K.G., & Lenz, M.W. (1990). Discrimination training for persons with developmental disabilities: A comparison of the task demonstration model and the standard prompting hierarchy. *Journal of Applied Behavior Analysis. 23,* 43-52. Reynolds, B.S., Newsome, C.D., & Lovaas, O.I., (1974). Auditory overselectivity in autistic children. *Journal of Abnormal Child Psychology, 2,* 253-263. Rincover A., & Koegel, R.L. (1975). Setting generality and stimulus control in autistic children. *Journal of Applied Behavior Analysis, 8,* 235-246.

Commenter	References
	Rincover, A., & Koegel, R.L. (1974). Classroom treatment of autistic children II: Individualized instruction in a group. *Journal of Abnormal Child Psychology*, 5, 113-126. Rincover, A., Newsome, C.D., Lovaas, O.I., & Koegel, R.L. (1977). Some motivational properties of sensory reinforcement in psychotic children. *Journal of Experimental Child Psychology.* 24, 312- 323. Risley, T.R., & Baer, D.M. (1973). Operant behavior modification: The deliberate development of behavior. In B. Caldwell, & H. Ricciuti (Eds.). *Review of child development research, Vol. III: Child development and social policy.* Chicago: University of Chicago Press. Risley, T.R., & Reynolds, N.J. (1970). Emphasis as a prompt for verbal imitation. *Journal of Applied Behavior Analysis. 3,* 185-190. Risley, T.R., & Wolf, M.M. (1966). Experimental manipulation of autistic behaviors and generalization into the home. In R. Ulrich, T. Stachnik, & J. Mabry, (Eds.) *Control of Human Behavior. Glenview, IL: Scott, Foresman.* Risley, T.R., & Wolf, M.M. (1967). Establishing functional speech in echolalic children. *Behavior Research and Therapy*, 5, 73-88. Risley, T.R., & Wolf, M.M. (1968). Establishing functional speech in echolalic children. In H.N. Sloane, & B.D. MacAulay (Eds.). *Operant procedures in remedial speech and language training.* Boston: Houghton, Mifflin. Rodgers, T.A., & Iwata, B.A. (1991). An analysis of error-correction procedures during discrimination training. *Journal of Applied Behavior Analysis, 24,* 775-782. Russo, D. C., Cataldo, M. F., & Cushing, P. J. (1981). Compliance training and behavioral covariation in the treatment of multiple behavior problems. *Journal of Applied Behavior Analysis, 14*, 209-222. Russo, D.C., & Koegel, R.L, (1977). A method for integrating an autistic child into a normal public school classroom. *Journal of Applied Behavior Analysis*, 10, 579-590. Russo, D.C., Koegel, R.L., & Lovaas, O.I. (1978). A comparison of human vs. automated instruction of autistic children. *Journal of Abnormal Child Psychology*, 6, 189-201. Sailor, W. (1971). Reinforcement and generalization of productive plural allomorphs in two retarded children. *Journal of Applied Behavior Analysis. 4,* 305-310. Sailor, W., & Taman, T. (1972). Stimulus factors in the training of prepositional usage in three autistic children. *Journal of Applied Behavior Analysis. 5,* 183-190. Sasso, G.M., & Rude, H.A. (1987). Unprogrammed effects of training high-status peers to interact with severely handicapped children. *Journal of Applied Behavior Analysis, 20,* 35-44. Sasso, G.M., Simpson, R.L., & Novak, C.G. (1985). Procedures for facilitating integration of autistic children in public school settings. *Analysis and Intervention with Developmental Disabilities*, 5, 233-246. Saunders, K. J., & Spradlin, J. E. (1990). Conditional discrimination in mentally retarded adults: The development of generalized skills. *Journal of The Experimental Analysis of Behavior,* **54** (3), 239-250. Schafer, M.S., Egel, A.L., & Neef, N.A. (1984). Training mildly handicapped peers to facilitate changes in the social interaction skills of autistic children. *Journal of Applied Behavior Analysis*, 17, 461-476. Schell, R.E., Stark, J., & Giddan, J. (1967). Development of language behavior in an autistic child. *Journal of Speech and Hearing Disorders, 32,* 51-64. Schreibman L, & Lovaas, O.I., (1973). Overselective response to social stimuli by autistic children. *Journal of Abnormal Child Psychology, 1,* 152-168. Schreibman, L. (1975). Effects of within-stimulus and extra-stimulus prompting on discrimination learning in autistic children. *Journal of Applied Behavior Analysis, 8,* 91-112. Schreibman, L., O'Neill, R.E., & Koegel, R.L. (1983). Behavioral training for siblings of autistic children. *Journal of Applied Behavior Analysis*, 16, 129-138. Schroeder, G.L., & Baer, D.M. (1972). Effects of concurrent and serial training on generalized vocal imitation in retarded children. *Developmental Psychology,* 6,

Commenter	References
	293-301. Schumaker, J. & Sherman, J. A. (1970). Training generative verb usage by imitation and reinforcement procedures. *Journal of Applied Behavior Analysis*, **3**, (4), 273-287. Shabani, D.B. & Fisher, W.E. (2006). Stimulus fading and differential reinforcement for the treatment of needle phobia in a youth with autism. *Journal of Applied Behavior Analysis*, 39, 449-452. Shipley-Benamou, R., Lutzker, J.R., & Taubman, M. (2002). Teaching daily living skills to children with autism through instructional video modeling. *Journal of Positive Behavioral Interventions,* 4, 165- 175. Solomon, R.W. & Wahler, R.G., (1973). Peer reinforcement control of classroom problem behavior. *Journal of Applied Behavior Analysis. 6,* 49-56. Stahmer, A.C., & Schreibman, L. (1992). Teaching children with autism: Appropriate play in unsupervised environments using a self-management treatment package. *Journal of Applied Behavior Analysis,* 25(2), 447-459. Stark, J., Giddan, J.J., & Meisel, J. (1968). Increasing verbal behavior in an autistic child. *Journal of Speech and Hearing Disorders, 3,* 42-48. Stevens-Long, J, & Rasmussen, M. (1974). The acquisition of simple and compound sentence structure in an autistic child. *Journal of Applied Behavior Analysis. 7,* 473-479. Stokes, T.F., Baer, D.M., & Jackson, R.L. (1974). Programming the generalization of a greeting response in four retarded children. *Journal of Applied Behavior Analysis*, 7, 599-610. Striefel, S., Wetherby, B., & Karlan, G. (1976). Establishing generalized verb-noun instruction-following skills in retarded children. *Journal of Experimental Child Psychology, 22,* 247-260. Sulzbacher, S.I., & Costello, J.M. (1970). A behavior strategy for language training of a child with autistic behaviors. *Journal of Speech and Hearing Disorders,* 35, 256-276. Taylor, B.A., Hughes, C.E., Richard, E., Hoch, H., & Rodriquez Coello, A. (2004). Teaching teenagers with autism to seek assistance when lost. *Journal of Applied Behavior Analysis*, 37, 79-82. Taylor, B.A., Levin, L., & Jasper, S. (1999). Increasing play-related statements in children with autism toward their siblings: Effects of video modeling. *Journal of Developmental and Physical Disabilities.* 11, 253-264. Thorp, D.M., Stahmer, A.C., & Schreibman, L. (1995). Effects of sociodramatic play training on children with autism. *Journal of Autism & Developmental Disorders,* 25(3), 265-282. Timm, M.A., Strain, P.S., & Eller, P.H. (1979). Effects of systematic, response-dependent fading and thinning procedures on the maintenance of child-child interaction. *Journal of Applied Behavior Analysis. 12,* 308. Touchette, P.E. (1971). Transfer of stimulus control: Measuring the moment of transfer. *Journal of the Experimental Analysis of Behavior,* 15, 347-354. Tryon, A.S., & Keane, S.P., (1986). Promoting imitative play through generalized observational learning in autistic-like children. *Journal of Abnormal Child Psychology*. 14, 537-549. Twardosz, S., & Sajwaj, T. (1972). Multiple effects of a procedure to increase sitting in a hyperactive, retarded boy. *Journal of Applied Behavior Analysis. 5,* 73-78. Valentino, A.L., Shillingsburg, M.A., & Call, N.A. (2012). Comparing the effects of echoic prompts and echoic prompts plus modeled prompts on intraverbal behavior. *Journal of Applied Behavior Analysis*, 45, 431-435. Varni, J.W., Lovaas, O.I., Koegel, R.L., & Everett, N.L. (1979). An analysis of observational learning in autistic and normal children. *Journal of Abnormal Child Psychology*. 7, 31-43.

Commenter	References
	Vollmer, T.R., Borrero, J.C., Lalli, J.S., & Daniel, D. (1999). Evaluating self-control and impulsivity in children with severe behavior disorders. *Journal of Applied Behavior Analysis*, 32, 451-466. Walker, H.M., & Buckley, N.K. (1972). Programming generalization and maintenance of treatment effects across time and across settings. *Journal of Applied Behavior Analysis*, 5, 209-224. Wells, K.C., Forehand, R., Hickey, K., & Green, K.D. (1977). Effects of a procedure derived from the overcorrection principle on manipulated and nonmanipulated behaviors. *Journal of Applied Behavior Analysis*, 10, 679-688. Werts, M.G., Caldwell, N.K., & Wolery, M. (1996). Peer modeling of response chains: Observational learning by students with disabilities. *Journal of Applied Behavior Analysis, 29,* 53-66. Werts, M.G., Caldwell, N.K., & Wolery, M. (1996). Peer modeling of response chains: Observational learning by students with disabilities. *Journal of Applied Behavior Analysis, 29,* 53-66. Wetherby, B. & Striefel, S. (1978). Application of miniature linguistic system of matrix training procedures. In R.L. Schiefelbusch (Ed.), *Language intervention strategies.* Baltimore, MD: University Park Press. Wheeler, A.J., & Sulzer, B. (1970). Operant training and generalization of a verbal response form in a speech-deficient child. *Journal of Applied Behavior Analysis.* 3, 139-147. Whitman, T.L., Zakaras, M., & Chardos, S. (1971). Effects of reinforcement and guidance procedures on instruction-following behavior in retarded children. *Journal of Applied Behavior Analysis.* 4, 283- 291. Williams, J.A., Koegel, R.L., & Egel, A.L. (1981). Response-reinforcer relationships and improved learning in autistic children. *Journal of Applied Behavior Analysis. 14,* 53-60. Wolf, M.M, Risley, T.R., Johnston, M., Harris, F., & Allen, E. (1967). Application of operant conditioning procedures to the behavior problems of an autistic child: A follow-up and extension. *Behavior Research and Therapy.* 5, 103-111. Wolf, M.M., Risley, T.R., & Mees, H. (1964). Application of operant conditioning procedures to the behaviour problems of an autistic child. *Behaviour Research and Therapy*, 1, 305-312. Young, J.M., Krantz, P.J., McClannahan, L.E., & Poulson, C.L. (1994). Generalized imitation and response-class formation in children with autism. *Journal of Applied Behavior Analysis,* 27, 685-697. Zimmerman, E.H., Zimmerman, J., & Russel, C.D. (1969). Differential effects of token reinforcement on instruction-following behavior in retarded students instructed as a group. *Journal of Applied Behavior Analysis.* 2, 101-112.
P	Mandell DS, et al. Racial/ethnic disparities in the identification of children with autism spectrum disorders. *American Journal of Public Health*. 2009 Mar;99(3):493-8. Paul T. Shattuck, PhD, et al. Timing of Identification Among Children with an Autism Spectrum Disorder *J. Am. Acad. Child Adoleesc. Psychiatry 2009; 48(5): 474-483*
S	Blew, P.A., Schwartz, I.S., & Luce, S.C. (1985). Teaching functional community skills to autistic children using nonhandicapped peer tutors. Journal of Applied Behavior Analysis. 18, 337-342. Charlop, M.H. (1983). The effects of echolalia on acquisition and generalization of receptive labeling in autistic children. Journal of Applied Behavior Analysis. 16, 111-127. Charlop, M.H., & Milstein, J.P. (1989). Teaching autistic children conversational speech using video modeling. Journal of Applied Behavior Analysis. 22, 275-286. Charlop, M.H., & Trasowech, J.E., (1991). Increasing autistic children's daily spontaneous speech. Journal of Applied Behavior Analysis. 24, 747-762.

Commenter	References
	Charlop, M.H., & Walsh, M.E. (1986). Increasing autistic children's spontaneous verbalizations of affection: An assessment of time delay and peer modelling procedures. Journal of Applied Behavior Analysis, 19, 307-314. Charlop, M.H., Kurtz, P.F., & Casey, F.G. (1990). Using aberrant behaviors as reinforcers for autistic children. Journal of Applied Behavior Analysis. 23, 163-182. Charlop, M.H., Kurtz, P.F., & Milstein, J.P. (1992). Too much reinforcement, too little behavior: Assessing task interspersal procedures in conjunction with different reinforcement schedules with autistic children. Journal of Applied Behavior Analysis, 25, 795-808. Charlop, M.H., Schreibman, L., & Thibodeau, M.G. (1985). Increasing spontaneous verbal responding in autistic children using a time delay procedure. Journal of Applied Behavior Analysis, 18, 155-166. Chew, Kristina. (June 2007). ABA and the Older Child, by Kristina Chew, Ph.D. Lovaas Institute Newsletter. Dunlap, G., & Koegel, R.L. (1980). Motivating autistic children through stimulus variation. Journal of Applied Behavior Analysis, 13, 619-627. Dunlap, G., & Johnson, Jean, (1985). Increasing the independent responding of autistic children with unpredictable supervision. Journal of Applied Behavior Analysis. 18, 227-236. Dunlap, G., Koegel, R.L., Johnson, Jean, & O'Neill, R.E. (1986). Maintaining performance of autistic clients in community settings with delayed contingencies. Journal of Applied Behavior Analysis. 20, 185-192. Dyer, K., Christian, W.P., & Luce, S.C. (1982). The role of response delay in improving the discrimination performance of autistic children. Journal of Applied Behavior Analysis, 15, 231-240. Egel, A. L., Richman, G. S., & Koegel, R. L. (1981). Normal peer models and autistic children's learning. Journal of Applied Behavior Analysis, 14, 3-12. Gaylord-Ross, R.J., Haring, T.G., Breen, C., & Pitts-Conway, V. (1984). The training and generalization of social interaction skills with autistic youth. Journal of Applied Behavior Analysis, 17, 229-248. Gena, A., Krantz, P., McClannahan, L.E., & Poulson, C.L. (1996). Training and generalization of affective behavior displayed by youth with autism. Journal of Applied Behavior Analysis, 29, 291-304. Handleman, J.S. (1979). Generalization by autistic-type children of verbal responses across settings. Journal of Applied Behavior Analysis, 12, 273-282. Ingenmey, R., & Van Houten, R. (1991). Using time delay to promote spontaneous speech in an autistic child. Journal of Applied Behavior Analysis, 24, 591-596. Kamps, D.M., Barbetta, P.M., Leonard, B.R., & Delquadri, J., (1994). Classwide peer tutoring: An integration strategy to improve reading skills and promote peer interactions among students with autism and general education peers. Journal of Applied Behavior Analysis, 27, 49-62. Koegel, R. L., Firestone, P. B., Kramme, K. W., & Dunlap, G. (1974). Increasing spontaneous play by suppressing self-stimulation in autistic children. Journal of Applied Behavior Analysis, 7, 521-528. Koegel, R.L, & Rincover, A., (1977). Research on the difference between generalization and maintenance in extra-therapy responding. Journal of Applied Behavior Analysis, 10, 1-12. Krantz, P.J., & McClannahan, L.E. (1993). Teaching children with autism to initiate to peers: Effects of a script-fading procedure. Journal of Applied Behavior Analysis, 26, 121-132. Larsson, Eric. (June 2007). Data-Based Research in Applied Behavior Analysis for Older Children with Autism. Lovaas Institute Newsletter. McGee, G.G., Krantz, P.J., & McClannahan, L.E. (1985). The facilitative effects of incidental teaching on preposition use by autistic children. Journal of Applied Behavior Analysis. 18, 17-32. Pierce, K., & Schreibman, L., (1995). Increasing complex social behaviors in children with autism: Effects of peer-implemented pivotal response training. Journal of Applied Behavior Analysis, 28. 285-296.

Commenter	References
T	Berge v. United States of America. Case 1:10-cv-00373-RBW, U.S. District Court for the District of Columbia. Jul 27, 2012, Doc. 119. K.G. v. Dudek. Case No. 11-20684-CIV-LENARD / O'SULLIVAN, U.S. District Court for the Southern District of Florida, Nov. 5, 2013, Doc 186. K.G. v. Dudek. Case No. 11-20684-CIV-LENARD / O'SULLIVAN, U.S. District Court for the Southern District of Florida, Nov. 5, 2013, Doc 187. K.G. v. Dudek. Case No. 11-20684-CIV-LENARD / O'SULLIVAN, U.S. District Court for the Southern District of Florida, Mar. 23, 2012. Transcript. Potter and Boyer v. Blue Cross Blue Shield of Michigan. Case 2:10-cv-14981-SJM-MJH, U.S. District Court for the Eastern District of Michigan Southern Division. Mar 30, 2013, Doc. 125.
V	**Comprehensive Technical Reviews of Research** Mudford, L., Blampied, N., Phillips, L., Harper, D., Foster, M., Church, J., Hunt, M., Prochnow, J., Rose, D., Arnold-Saritepe, A., Peters, H., Lie, E., Jeffrey, K., Messick, E., Sumpter, C., McEwan, J., & Wilczynski S. (2009). *Technical review of published research on applied behaviour analysis interventions for people with autism spectrum disorders.* Wellington, New Zealand: Ministry of Education. Available at http://www.educationcounts.govt.nz/publications/special_education/61210/1 National Autism Center (2009). *National Standards Project Findings and Conclusions.* Randolph, MA: Author. New York State Department of Health Early Intervention Program (1999). *Clinical Practice Guideline: Autism/Pervasive Developmental Disorders--Assessment and Intervention for Young Children (Age 0-3 Years).* Health Education Services, P.O.Box 7126, Albany, NY 12224 (1999 Publication No. 4216). **Systematic Reviews, Meta-Analyses, and Other Analyses of Aggregated ABA Clinical Trials of Focused ABA Interventions** ***NOTE:*** Articles with "developmental disabilities" and "intellectual disabilities" in the titles or abstracts included studies involving participants with ASD diagnoses. **Use of a short-term inpatient model to evaluate aberrant behavior: Outcome data summaries from 1996 to 2001.** Jennifer M. Asmus, Joel E. Ringdahl, Jennifer A. Sellers, Nathan A. Call, Marc S. Andelman, and David P. Wacker, The University Of Iowa *Journal of Applied Behavior Analysis* (2004) *37* 283–304 **A review of behavioral interventions for the treatment of aggression in individuals with developmental disabilities.** Julie Brosnan and Olive Healy, National University of Ireland, Galway, Ireland *Research in Developmental Disabilities 32* (2011) 437–446 Aggression can present as a significant problem behavior in individuals with a diagnosis of developmental disability. Much research has focused on the prevalence of aggression in individuals with varying degrees of severity of intellectual disability (AD), autism spectrum disorders (ASD) and co-morbidity of ID and ASD. Research has also focused on the impact of aggressive behavior on individuals' development including cognitive, adaptive and social functioning. The literature on Applied Behavior Analysis provides abundant examples of various interventions that are effective in reducing or eliminating aggressive behavior across a range of ages and degrees of developmental disabilities. Many interventions report success using antecedent alterations, reinforcement-based strategies and consequence manipulations. The current review provides a focused, comprehensive examination of aggressive behavior intervention research for individuals with developmental disabilities aged 3–18 years published between 1980 and 2009. **Efficacy of behavioral interventions for reducing problem behavior in persons with autism: A quantitative synthesis of single-subject research.** Jonathan M. Campbell, Department of Psychology, University of Memphis, Memphis, TN, USA *Research in Developmental Disabilities 24* (2003) 120-138 The efficacy of behavioral interventions for problem behavior in persons with autism was reviewed. One hundred and seventeen published articles representing 181 individuals with autism were examined. Articles were selected from 15 journals. Participant, treatment, and experimental variables were evaluated. Three effect sizes were calculated for each article. Behavioral treatments are effective in reducing problematic behaviors in individuals with autism. Type of target behavior and type of treatment did not moderate the average effect of treatment. As measured by percentage of zero data (PZD), three variables were predictive of behavioral suppression beyond that accounted for by behavioral topography and treatment type. Reliability of observation and number of treatment data points were positively related to PZD scores. Treatments based on experimental functional analysis (EFA) produced higher average PZD scores than treatments that did not include an EFA. The implications of the findings, study limitations, and suggestions for

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	future research are discussed. **A review of research on procedures for teaching safety skills to persons with developmental disabilities.** Dennis R. Dixon, Ryan Bergstrom, Marlena N. Smith, and Jonathan Tarbox, Center for Autism and Related Disorders, United States *Research in Developmental Disabilities 31* (2010) 985–994 Safety skills are an important but often neglected area of training for persons with developmental disabilities (DD). The present study reviewed the literature on teaching safety skills to persons with DD. Safety skills involve a variety of behaviors such as knowing how to cross the street or what to do in case of a house fire. A number of studies have been conducted on teaching these skills to individuals with DD. The studies reviewed have varying degrees of success and demonstrate varying degrees of generalization, but the general finding has been that prompting, reinforcement, and role-playing are effective teaching procedures across a variety of participants, skills, and settings. **Communication intervention for children with autism: A review of treatment efficacy** Howard Goldstein, Florida State University.*Journal of Autism and Developmental Disorders* (2002) *32* 373-396 Empirical studies evaluating speech and language intervention procedures applied to children with autism are reviewed, and the documented benefits are summarized. In particular, interventions incorporating sign language, discrete trial training, and milieu teaching procedures have been used successfully to expand the communication repertoires of children with autism. Other important developments in the field stem from interventions designed to replace challenging behaviors and to promote social and scripted interactions. The few parent and classroom training studies that included language measures also are analyzed. This article seeks to outline the extent to which previous research has helped identify a compendium of effective instructional practices that can guide clinical practice. It also seeks to highlight needs for further research to refine and extend current treatment approaches and to investigate more comprehensive treatment packages. **Initial functional analysis outcomes and modifications in pursuit of differentiation: A summary of 176 inpatient cases.** Louis P. Hagopian, Griffin W. Rooker, Joshua Jessel, and Iser G. Deleon, Kennedy Krieger Institute and Johns Hopkins University School Of Medicine *Journal of Applied Behavior Analysis* (2013) *46* 88–100 The functional analysis (FA) described by Iwata, Dorsey, Slifer, Bauman, and Richman (1982/1994) delineated not only a set a specific procedures, but also a model that involves the use of analogue conditions wherein antecedent and consequent variables are systematically manipulated. This consecutive caseseries analysis describes FAs of 176 individuals with intellectual disabilities who had been admitted to an inpatient unit for severe problem behavior. Following an initial standardized FA, additional modifications were performed in pursuit of differentiation. Ultimately, a function was identified in 86.9% of the 176 cases and in 93.3% of the 161 cases for which the FA, if necessary, was modified up to 2 times. All modifications were documented and classified as involving changes to antecedents, consequences, or design (or some combination of these). Outcomes for each type of modification are reported. The results support the utility of ongoing hypothesis testing through individualized modifications to FA procedures, and provide information regarding how each type of modification affected results. **Identifying empirically supported treatments for pica in individuals with intellectual disabilities.** Louis P. Hagopian, Griffin W. Rooker, and Natalie U. Rolider, The Kennedy Krieger Institute, Johns Hopkins University School of Medicine *Research in Developmental Disabilities 32* (2011) 2114–2120 The purpose of the current study was to critically examine the existing literature on the treatment of pica displayed by individuals with intellectual disabilities. Criteria for empirically supported treatments as described by Divisions 12 and 16 of APA, and adapted for studies employing single-case designs were used to review this body of literature. A total of 34 treatment studies were identified, 25 of which were well designed and reported at least an 80% reduction in pica (21 studies reported 90% or greater reduction in pica). Results indicated that behavioral treatments in general, and treatments involving the combination of reinforcement and response reduction procedures in particular, can be designated as well-established treatments for pica exhibited by

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	individuals with intellectual disabilities. **A multilevel meta-analysis of single-case and small-n research on interventions for reducing challenging behavior in persons with intellectual disabilities** M. Heyvaert , B. Maes, W. Van den Noortgate, S. Kuppens, and P. Onghena, Faculty of Psychology and Educational Sciences, Katholieke Universiteit Leuven, Belgium *Research in Developmental Disabilities 33* (2012) 766–780 The effectiveness of different interventions for challenging behavior (CB) in persons with intellectual disabilities (ID) was reviewed by means of a two-phase study. First, a systematic review of 137 meta-analyses and reviews on group study interventions for CB in persons with ID was conducted. Based on this review, hypotheses concerning the effectiveness of divergent interventions for CB and concerning the impact of variables moderating treatment effectiveness were systematically generated. Second, these hypotheses were tested by means of a multilevel meta-analysis of single-case and small-n research. Two hundred and eighty-five studies reporting on 598 individuals were examined. The average treatment effect was large and statistically significant. However, this effect varied significantly over the included studies and participants. Compared to the meta-analyses and reviews focusing on group-studies in this research domain, the results of the present multilevel meta-analysis of single-case and small-n intervention research provided more detailed knowledge on which specific CB and intervention components moderate the interventions' effectiveness. **Identifying empirically supported treatments for phobic avoidance in individuals with intellectual disabilities.** Heather K. Jennett and Louis P. Hagopian, Kennedy Krieger Institute and Johns Hopkins School of Medicine *Behavior Therapy 39* (2008) 151–161 This paper reviews the literature regarding the treatment of phobic avoidance in individuals with intellectual disabilities. Criteria for classifying interventions as empirically supported, developed by the American Psychological Association (APA) Division 12 Task Force on Promotion and Dissemination of Psychological Procedures, were used. For studies employing single case experimental designs, criteria developed by APA Division 16 (Kratochwill & Stoiber, 2002; Shernoff, Kratochwill,& Stoiber, 2002) were used to supplement Division 12 criteria. Results indicate that behavioral treatment can be designated as a well established treatment for phobic avoidance in individuals with intellectual disabilities. **An analysis of functional communication training as an empirically supported treatment for problem behavior displayed by individuals with intellectual disabilities.** Patricia F. Kurtz a,b,*, Eric W. Boelter c, David P. Jarmolowicz d, Michelle D. China, Louis P. Hagopian a,b a Kennedy Krieger Institute, United States b The Johns Hopkins University School of Medicine, United States c Seattle Children's Autism Center, United States d Virginia Tech Carilion Research Institute, United States *Research in Developmental Disabilities 32* (2011) 2935–2942 This paper examines the literature on the use of functional communication training (FCT) as a treatment for problem behavior displayed by individuals with intellectual disabilities (ID). Criteria for empirically supported treatments developed by Divisions 12 and 16 of the American Psychological Association (Kratochwill & Stoiber, 2002; Task Force, 1995) and adapted by Jennett and Hagopian (2008) for evaluation of single-case research studies were used to examine the support for FCT. Results indicated that FCT far exceeds criteria to be designated as a well-established treatment for problem behavior exhibited by children with ID and children with autism spectrum disorder, and can be characterized as probably efficacious with adults. **Treatment of elopement in individuals with developmental disabilities: A systematic review.** Russell Lang a, Mandy Rispoli a, Wendy Machalicek b, Pamela J. White a, Soyeon Kang a, Nigel Pierce a, Austin Mulloy a, Tina Fragale a, Mark O'Reilly a, Jeff Sigafoos c, Giulio Lancioni d a The Meadows Center for Preventing Educational Risk, The University of Texas at Austin, Austin, TX, USA b Portland State University, Portland, Oregon, USA c Victoria University of Wellington, New Zealand d University of Bari, Italy *Research in Developmental Disabilities 30* (2009) 670–681 We reviewed studies involving the treatment of elopement in individuals with developmental disabilities. Systematic searches of three electronic databases, journals, and reference lists identified 10 studies meeting the inclusion criteria. These studies were evaluated in terms of: (a) participants, (b) procedures used to assess elopement, (c) intervention procedures, (d) results of the intervention, and (e) certainty of evidence. Across the 10 studies, intervention was

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	provided to a total of 53 participants aged 3–47 years. Assessment procedures included anecdotal staff reports, participant interviews, direct observation, and modified analog functional analysis. Intervention approaches included differential reinforcement, extinction, functional communication training, response blocking, non-contingent reinforcement, shaping, and scheduled exercise. Positive outcomes were reported in 80% of the reviewed studies. The evidence base suggests that function-based assessment (e.g. functional analysis procedures) and function-based treatments (e.g. functional communication training) may be most effective in the treatment of elopement. **Evidence to practice: Treatment of anxiety in individuals with autism spectrum disorders.** Russell Lang, Richard Mahoney, Farah El Zein, Elizabeth Delaune, and Megan Amidon, Texas State University-San Marcos, TX, USA *Neuropsychiatric Disease and Treatment* (2011*) 7* 27–30 Clinical question: What treatment improves social interactions and reducesreports of anxiety symptoms in individuals with autism spectrum disorders (ASD) and a co-occurring anxiety disorder? Results: Systematic reviews and randomized clinical trials suggest that cognitive behavior therapy in tandem with direct instruction of social skills using applied behavior analysis intervention components may be effective for treating anxiety in individuals with high functioning ASD. For individuals with ASD, an anxiety disorder, and an intellectual disability, systematic desensitization may be effective. Implementation: Intervention should emphasize teaching social skills. Reinforcers (i.e., rewards based upon the client's interests) should be used to encourage participation in therapy. Treatment should incorporate visual aides and family involvement. Intervention components involving abstract concepts, visualization, and discussions of emotions are less useful given difficulties in abstract reasoning and communication inherent to ASD. **The effectiveness of intervention on the behavior of individuals with autism: A meta-analysis using percentage of data points exceeding the median of baseline phase (PEM).** Hsen-Hsing Ma, National Chengchi University, Taiwan *Behavior Modification* (2009) *33* 339-359 The aim of the present study is to demonstrate the percentage of data points exceeding the median of baseline phase (PEM) approach using data on autism treatment for illustrative purposes to compare the effectiveness of different interventions on the problem behaviors of individuals with autism. Electronic databases such as The ProQuest and Google were searched. A total of 163 articles were located, producing 1,502 effect sizes. The results demonstrate that five highly effective intervention strategies were priming, self-control, training, positive reinforcement and punishment, and presenting preferential activities. The least effective strategy was to teach perspective taking skills. The PEM approach is recommended for use in meta-analysis for single case experimental designs. **Social skills interventions for individuals with autism: Evaluation for evidence-based practices within a best evidence synthesis framework.** Brian Reichow and Fred R. Volkmar, Yale University Child Study Center. *Journal of Autism and Developmental Disorders* (2010) *40* 149–166 This paper presents a best evidence synthesis of interventions to increase social behavior for individuals with autism. Sixty-six studies published in peer-reviewed journals between 2001 and July 2008 with 513 participants were included. The results are presented by the age of the individual receiving intervention and by delivery agent of intervention. The findings suggest there is much empirical evidence supporting many different treatments for the social deficits of individuals with autism. Using the criteria of evidence-based practice proposed by Reichow et al. (Journal of Autism and Developmental Disorders, 38:1311– 1318, 2008), social skills groups and video modeling have accumulated the evidence necessary for the classifications of established EBP and promising EBP, respectively. Recommendations for practice and areas of future research are provided. **Meta-analyses of Studies of Bona Fide Early Intensive ABA Intervention Meta-analysis of early intensive behavioral intervention for children with autism.** Sigmund Eldevik, School of Psychology, Bangor University; Faculty of Behavioral Science, Akershus University College; and Highfield Centre Richard P. Hastings and J. Carl Hughes, School of Psychology, Bangor University Erik Jahr, Akershus University Hospital Svein Eikeseth, Faculty of Behavioral Science, Akershus University College Scott Cross, Lovaas Institute for Early Intervention *Journal of Clinical Child & Adolescent Psychology* (2009) *38* 439–450 A systematic literature search for studies reporting effects of Early Intensive Behavioral Intervention identified 34 studies, 9 of which were controlled

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	designs having either a comparison or a control group. We completed a meta-analysis yielding a standardized mean difference effect size for two available outcome measures: change in full-scale intelligence and/or adaptive behavior composite. Effect sizes were computed using Hedges's g. The average effect size was 1.10 for change in full-scale intelligence (95% confidence interval, .87, 1.34) and .66 (95% confidence interval, .41, .90) for change in adaptive behavior composite. These effect sizes are generally considered to be large and moderate, respectively. Our results support the clinical implication that at present, and in the absence of other interventions with established efficacy, Early Intensive Behavioral Intervention should be an intervention of choice for children with autism. **Using participant data to extend the evidence base for intensive behavioral intervention for children with autism.** Sigmund Eldevik, Akershus University College, Lillestrom, Norway Richard P. Hastings and J. Carl Hughes, Bangor University, Bangor, Wales Erik Jahr, Akershus University Hospital, Lorenskog, Norway Svein Eikeseth, Akershus University College, Lillestrom, Norway Scott Cross, Lovaas Institute for Early Intervention, Culver City, CA, USA. *American Journal on Intellectual and Developmental Disabilities* (2010) *115* 381–405 We gathered individual participant data from 16 group design studies on behavioral intervention for children with autism. In these studies, 309 children received behavioral intervention, 39 received comparison interventions, and 105 were in a control group. More children who underwent behavioral intervention achieved reliable change in IQ (29.8%) compared with 2.6% and 8.7% for comparison and control groups, respectively, and reliable change in adaptive behavior was achieved for 20.6% versus 5.7% and 5.1%, respectively. These results equated to a number needed to treat of 5 for IQ and 7 for adaptive behavior and absolute risk reduction of 23% and 16%, respectively. Within the behavioral intervention sample, IQ and adaptive behavior at intake predicted gains in adaptive behavior. Intensity of intervention predicted gains in both IQ and adaptive behavior.
X, Y	Asmus, J. M., Ringdahl, J. E., Sellers, J. A., Call, N. A., Andelman, M. S., & Wacker, D. P. (2004). Use of a short-term inpatient model to evaluate aberrant behavior: Outcome data summaries from 1996 to 2001. *Journal of Applied Behavior Analysis*, *37,* 283–304. Brosnan, J., & Healy, O. (2011). A review of behavioral interventions for the treatment of aggression in individuals with developmental disabilities. *Research in Developmental Disabilities, 32*, 437–446. Campbell, J. M. (2003). Efficacy of behavioral interventions for reducing problem behavior in persons with autism: A quantitative synthesis of single-subject research. *Research in Developmental Disabilities, 24,* 120-138. Dixon, D. R., Bergstrom, R. Smith, M. N., & Tarbox, J. (2010). A review of research on procedures for teaching safety skills to persons with developmental disabilities. *Research in Developmental Disabilities, 31,* 985–994. Eldevik, S., Hastings, R. P., Hughes, J. C., Jahr, E., Eikeseth, S., & Cross, S. (2010). Using participant data to extend the evidence base for intensive behavioral intervention for children with autism. *American Journal on Intellectual and Developmental Disabilities, 115,* 381–405. Eldevik, S., Hastings, R. P., Hughes, J. C., Jahr, E., Eikeseth, S., & Cross, S. (2009). Meta-analysis of early intensive behavioral intervention for children with autism. *Journal of Clinical Child & Adolescent Psychology, 38,* 439–450. Goldstein, H. (2002). Communication intervention for children with autism: A review of treatment efficacy. *Journal of Autism and Developmental Disorders, 32,* 373-396. Hagopian, L. P., Rooker, G. W., Jessel, J., & Deleon, I. G. (2013) Initial functional analysis outcomes and modifications in pursuit of differentiation: A summary of 176 inpatient cases. *Journal of Applied Behavior Analysis*, *46,* 88–100. Hagopian, L. P., Rooker, G. W., & Rolider, N. U. (2011). Identifying empirically supported treatments for pica in individuals with intellectual disabilities. *Research in Developmental Disabilities, 32,* 2114–2120. Heyvaert, M., Maes, B., Van den Noortgate, W., Kuppens, S., & Onghena, P. (2012). A multilevel meta-analysis of single-case and small-n research on interventions

Commenter	References
	for reducing challenging behavior in persons with intellectual disabilities. *Research in Developmental Disabilities, 33*, 766–780. Jennett, H. K., & Hagopian, L. P. (2008). Identifying empirically supported treatments for phobic avoidance in individuals with intellectual disabilities. *Behavior Therapy, 39,* 151–161. Kurtz, P. F., Boelter, E. W., Jarmolowicz, D. P., Chin, M. D., & Hagopian, L. P. (2011). An analysis of functional communication training as an empirically supported treatment for problem behavior displayed by individuals with intellectual disabilities. *Research in Developmental Disabilities, 32,* 2935–2942. Lang, R., Rispoli, M., Machalicek, W., White, P. J., Kang, S., Pierce, N., Mulloy, A., Fragale, T., O'Reilly, M., Sigafoos, J., & Lancioni, G. (2009). Treatment of elopement in individuals with developmental disabilities: A systematic review. *Research in Developmental Disabilities, 30,* 670–681. Lang, R., Mahoney, R., El Zein, F., Delaune, E., & Amidon, M. (2011). Evidence to practice: Treatment of anxiety in individuals with autism spectrum disorders. *Neuropsychiatric Disease and Treatment, 7,* 27–30. Ma, H. (2009). The effectiveness of intervention on the behavior of individuals with autism: A meta-analysis using percentage of data points exceeding the median of baseline phase (PEM). *Behavior Modification, 33,* 339-359. Mudford, L., Blampied, N., Phillips, L., Harper, D., Foster, M., Church, J., Hunt, M., Prochnow, J., Rose, D., Arnold-Saritepe, A., Peters, H., Lie, E., Jeffrey, K., Messick, E., Sumpter, C., McEwan, J., & Wilczynski S. (2009). *Technical review of published research on applied behaviour analysis interventions for people with autism spectrum disorders.* Wellington, New Zealand: Ministry of Education. Available at http://www.educationcounts.govt.nz/publications/special_education/61210/1 National Autism Center (2009). *National Standards Project Findings and Conclusions.* Randolph, MA: Author. New York State Department of Health Early Intervention Program (1999). *Clinical Practice Guideline: Autism/Pervasive Developmental Disorders-- Assessment and Intervention for Young Children (Age 0-3 Years).* Health Education Services, P.O.Box 7126, Albany, NY 12224 (1999 Publication No. 4216). Reichow, B., & Volkmar, F. R. (2010). Social skills interventions for individuals with autism: Evaluation for evidence-based practices within a best evidence synthesis framework. *Journal of Autism and Developmental Disorders*, *40,* 149–166. Shabani, D. B., & Fisher, W. W. (2006). Stimulus fading and differential reinforcement for the treatment of needle phobia in a youth with autism. *Journal of Applied Behavior Analysis*, *39*(4), 449-452.
BB	American Psychological Association (2002). Criteria for evaluating treatment guidelines. *American Psychologist, 57,* 1052-1059. Dube, W. V., MacDonald, R. P. F., Mansfield, R. C., Holcomb, W., & Ahearn, W. H. (2004). Toward a behavioral analysis of joint attention. *The Behavior Analyst, 27,* 197-207. Fisher, W. W., & Mazur, J. E. (1997). Basic and applied research on choice responding. *Journal of Applied Behavior Analysis, 30,* 387-410. Horner, R. H., Carr, E. G., Halle, J., McGee, G., Odom, S., & Wolery, M. (2005). The use of single-subject research to identify evidence-based practice in special education. *Exceptional Children, 71,* 165-179. Iwata, B. A., Pace, G. M., Dorsey, M. F., Zarcone, J. R., Vollmer, T. R., Smith, R. G. et al. (1994). The functions of self-injurious behavior: An experimental-epidemiological analysis. *Journal of Applied Behavior Analysis, 27,* 215-240. Kodak, T., & Piazza, C. C. (2008). Assessment and treatment of feeding and sleeping disorders in children diagnosed with developmental disabilities. *Child and Adolescent Psychiatric Clinics of North America, 17,* 887-906. Kurtz, P. F., Chin, M. D., Huete, J. M., Tarbox, R. S. F., O'Conner, J. T., Paclawskyj, T., & Rush, K. S. (2003). Functional analysis and treatment of self-injurious behavior in young children: A summary of 30 cases. *Journal of Applied Behavior Analysis, 36,* 205-219. Lerman, D. C., & Iwata, B. A. (1996). Developing a technology for the use of operant extinction in clinical settings: An examination of basic and applied research.

Commenter	References
	Journal of Applied Behavior Analysis, 29, 345-382. Lerman, D. C., & Vorndran, C. M. (2002). On the status of knowledge for using punishment: Implications for treating behavior disorders. *Journal of Applied Behavior Analysis, 35,* 431-464. Matson, J., Benavidez, D., Compton, L., Paclawskyj, J., & Baglio, C. (1996). Behavioral treatment of autistic persons: A review of research from 1980 to the present. *Research in Developmental Disabilities, 17,* 433-465. Petursdottir, A. I., & Carr, J. E. (2011). A review of recommendations for sequencing receptive and expressive identification instruction. *Journal of Applied Behavior Analysis, 44,* 859-876. Tiger, J. H., Hanley, G. P., & Bruzek, J. (2008). Functional communication training: A review and practical guide. *Behavior Analysis in Practice, 1,* 16-23. Wong. C. S. (2013). A play and joint attention intervention for teachers of young children with autism: A randomized controlled pilot study.

References from Invited Presenters (September 12, 2013 EbGS Meeting)

Presenter	Reference
Dr. Gina Green, Ph.D., BCBA-D, Association of Professional Behavior Analysts	• Larson, E. B. (1990). N-of-1 clinical trials: A technique for improving medical therapeutics. The Western Journal of Medicine, 1, 52-56. • Guyatt, G.H. et al (1988). A clinician's guide for conducting randomized trials in individual patients. Canadian Medical Association Journal, 139, 497-503. • Guyatt, G.H. et al (2000). Users' guides to the medical literature: XXV. Evidence-based medicine: Principles for applying the users' guides to patient care. JAMA, 284, 1290-1296. • Luce BR, Kramer JM, Goodman SN, Connor JT, Tunis S, Whicher D, Schwartz JS. (2009). Rethinking randomized clinical trials for comparative effectiveness research: the need for transformational change. Annals of Internal Medicine, 151(3), 206-209. • National Autism Center National Standards Project • New Zealand Ministries of Health and Education • New York Department of Health Early Intervention Program • National Professional Development Center for ASD
Dr. Brian Reichow, Ph.D., BCBA-D, Yale Child Study Center, AJ Pappanikou Center for Excellence in Developmental Disabilities	• Reichow B, Barton EE, Boyd BA, Hume K. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD009260. DOI: 10.1002/14651858.CD009260.pub2. • Sackett et al., 1995
Dr. Louis P. Hagopian, Ph.D., BCBA-D Johns Hopkins University School of Medicine; Kennedy Krieger Institute	• Didden et al., (1997) • Campbell (2003) • Hanley et al., 2003 • Iwata et al., 1994, FBA of self-injury • Mueller, et al., 2001, FBA in school • Hagopian et al., 2013, FBA of problem behavior • Kahng, S., Iwata, B. A., & Lewin, A. B. (2002). Behavioral Treatment of Self-Injury, 1964 to 2000. American Journal on Mental Retardation, 107, 212-221. • Campbell et al., 2003 • Harvey et al., 2009. Updating a meta-analysis of intervention research with challenging behaviour: Treatment validity and standards of practice. Journal of Intellectual and Developmental Disability, 34, 67–80 • Kurtz et al., 2011. An analysis of functional communication training as an empirically supported treatment for problem behavior displayed by individuals with intellectual disabilities. *Research in developmental disabilities* ;32(6):2935-42. • Carr JE, Severtson JM, Lepper TL. (2009). Noncontingent reinforcement is an empirically supported treatment for problem behavior exhibited by

Presenter	Reference
	individuals with developmental disabilities. Res Dev Disabil. 2009 Jan-Feb;30(1):44-57. doi: 10.1016/j.ridd.2008.03.002. • Hagopian et al., 2011 • Jennett et al., 2011 • Asmus et al. 2004 • Rooker GW, Jessel J, Kurtz PF, Hagopian LP. Functional communication training with and without alternative reinforcement and punishment: An analysis of 58 applications. J Appl Behav Anal. 2013 Aug 22. doi: 10.1002/jaba.76. [Epub ahead of print] • Kurtz et al., in press, ABA treatment with parents

SUMMARY CONCLUSIONS with additional language for consideration

Children age 12 and younger

Applied behavior analysis (ABA), including early intensive behavioral intervention (EIBI), is recommended for coverage[1] for treatment of autism spectrum disorder[2] (*strong recommendation*).

> Rationale: This strength of recommendation was based on sufficient (moderate quality) evidence and expert input, including testimony on parent/caregiver values and preferences.

Specifically, comprehensive ABA, including EIBI, is recommended for coverage for an average of 20~~up to 25~~ hours per week of behavior technician and an average of 7 hours per week of behavior analyst services for a maximum of 3 years.

> Rationale: In studies showing benefit, interventions ranged from less than two to 6~~4~~0 hours per week and had a studied duration of 10 weeks to more than three years. No specific minimum duration or intensity has been determined to be required for efficacy. 25 hours a week was chosen based on SB 365 as well as efficacy demonstrated in studies with 25 hours per week, without evidence of increased intensity beyond this level yielding improved outcomes.

Initial coverage of comprehensive ABA should be provided for up to six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the intervention(s) under scrutiny, over and beyond gains that would be expected to arise from maturation alone) using a standardized, multimodal assessment, no more frequently than every six months *(strong recommendation).* Examples of standardized criterion-referenced and norm-referenced assessments include tests of adaptive functioning, developmental assessments, tests of cognitive skills, tests of communication skills, behavior checklists, and autism symptom rating scales. The schedule of administration of the various assessments should follow the publisher's recommendations. The schedule of administration of the various assessments should follow the publisher's recommendations. ~~Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).~~

> Rationale: Ensuring that patients are making meaningful progress is important to ensure quality outcomes and effective use of resources. The six month assessment

[1] These conclusions apply to the Oregon Health Plan as governed by the Prioritized List of Health Services and to no other health plan.
[2] Autism spectrum disorder should be diagnosed by a qualified health care professional according to DSM-5 criteria.

was chosen based on expert input to allow for sufficient time for progress while not being burdensome to providers and plans.

If comprehensive ABA is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then targeted behavioral interventions (including focused ABA*) are recommended for coverage to address specific problem areas as needed, ~~up to~~for a minimum of 8 hours per month ~~(up to age 12, 18 or no limit)~~ of behavior analyst services and up to 8 hours per week of behavior technician services. *(weak recommendation).*

Rationale: Not all autistic children require comprehensive therapy and focused interventions will be appropriate for many, or appropriate for those who have completed 3 years of intensive intervention. Additionally, there is not good data that focused ABA is more effective than other types of interventions (although there is even less evidence to support any alternative treatment modality) -and so the language is open to other types of targeted behavioral interventions as well. Eight hours was chosen based on a wide range of intensity in the literature, expert input, and previous HERC Prioritized List guideline precedent.

Parent/caregiver involvement and training is recommended to be a component of treatment *(strong recommendation).*

Rationale: Evidence and expert input indicated that parental involvement in ABA is a key part of effective treatment. Where parent capacity for supporting treatment is limited, inpatient or day treatment should be considered.

~~Children~~ Individuals ages 13 and older

Comprehensive ABA is not recommended for coverage for treatment of autism spectrum disorder in persons over the age of 12 (*weak recommendation*).

Rationale: There is insufficient evidence to support intensive ABA treatment at older ages, although there is no experimentally controlled evidence to indicate a decline in effectiveness with age, even less evidence to support any alternative treatment modality, and strong evidence that a failure to treat autism can result in serious disability.~~.~~

For ~~children *(and adults?)*~~individuals age 13 and older, targeted behavioral interventions, including focused ABA*, is recommended for coverage for ~~up to~~a minimum of 8 hours per

month of behavior analyst services and up to an average of ~~up to~~ 8 hours per week of behavior technician services, to address specific problem behaviors (*weak recommendation*

Rationale: There is insufficient evidence to support effective interventions in this age group. However, problem behaviors (such as aggression, self-injury, property destruction, pica, or other significant impairment in day to day living) can be challenging to the individual, caregivers, and society and may result in serious disability if left untreated, making a clinical trial unreasonable. It is reasonable to consider targeted interventions for specific problem behaviors with clear objectives and ongoing proof of medical necessity.

*Focused ABA is defined as targeted ABA-based interventions addressing 1-2 problem behaviors (e.g. self-injurious behavior) for a period of ~~no longer than 2~~6 months which includes the initial assessment phase and transitional programming phase to ensure sustained benefit. The interventions should involve predefined behavioral objectives that would result in socially important and sustainable outcomes for the individual. Ongoing coverage of targeted behavioral interventions is based on evidence of documented improvement (as a result of the intervention) and ongoing need for services, ~~at least every 30 XX days~~every six months. *(weak recommendation)*

Parent/caregiver involvement and training is recommended to be a component of focused ABA treatments. *(strong recommendation).*

Rationale: Evidence and expert input indicated that parental involvement in ABA is a key part of effective treatment.

Behavior analytic assessment and analysis is recommended for coverage for an initial period of 40 hours to establish the medical necessity of either comprehensive or focused ABA treatment and to identify treatment targets.

Rationale: Behavior analytic services are recommended for an initial period to collect direct observational data on the patient's levels of functioning and severity of needs, evaluate current levels of services and supports, establish a baseline for evaluation of continued coverage, identify and prioritize treatment targets, and recommend medically necessary treatment procedures, settings, and intensity.

Inpatient ABA treatment is recommended where parent capacity for active involvement in treatment is limited, the risk to the client's health is significant (e.g., due to self injury, aggression, pica, elopement), or treatment is determined to be medically necessary to produce gains in skills such as self-care, cooperation with medical and dental procedures, functional communication, or personal safety. A decision to discharge the patient should be based upon treatment team determination that the client is behaviorally stable and no

longer a risk to self or others when treatment is implemented by trained care providers, the treatment has been generalized and modified to the extent it can be implemented in community settings, and care providers have been trained to implement the ABA interventions correctly and consistently *(strong recommendation).*

Note: The evidence for the treatment of conditions comorbid with autism spectrum disorder is beyond the scope of this evidence summary.

SUMMARY CONCLUSIONS with revisions and additional language for consideration

Report by ABA Experts Eric Larsson, Gina Green, and Louis Hagopian (4/16/2014)

Children ages 12 and younger

Comprehensive applied behavior analysis (ABA) treatment, including early intensive behavior analytic intervention (EIBI), is recommended for coverage[1] for treatment of autism spectrum disorder[2] in children age 12 years and younger (*strong recommendation*).

> Rationale: This recommendation was based on sufficient (moderate quality) evidence and expert input, including testimony on parent/caregiver values and preferences.

Specifically, comprehensive ABA treatment, including EIBI, is recommended for coverage for a minimum of 20 hours per week of behavior technician services directly to the patient and a minimum of 7 hours per week of direct behavior assessment, monitoring, staff and parent training, analysis and treatment planning, and clinical oversight by a professional behavior analyst. Additional hours may be authorized on an individual basis when medically necessary. Comprehensive ABA treatment may be delivered in inpatient or outpatient settings, or a combination thereof. The duration of treatment shall be determined by the ABA treatment team based on evidence of medical necessity to prevent serious disability (as defined by the American Academy of Pediatrics, June 2013) and patient progress.

> Rationale: In studies of comprehensive ABA interventions for young children with ASD, intensity ranged from 10 to 40+ hours per week for a duration of one to three or more years. The best available evidence indicates that EIBI of at least 30 hours per week for at least two years produces optimal outcomes (Eldevik et al., 2010). Research and best practices in ABA treatment indicate that for children with ASD who make sufficient gains, the number of ABA treatment hours per week is generally reduced when the child is being transitioned to typically available services. The recommendation above is based on SB 365 and expert input. The minimum intensity and duration reflect the lower end of the range of comprehensive ABA intervention that research has shown to be efficacious for preventing serious disability.

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[1] These conclusions apply to the Oregon Health Plan as governed by the Prioritized List of Health Services and to no other health plan.

[2] Autism spectrum disorder should be diagnosed by a qualified health care professional according to DSM-5 criteria.

Initial coverage of comprehensive ABA treatment should be provided for up to six months. Ongoing coverage should be based on evidence of medical necessity and demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the intervention(s) over and above gains that would be expected from maturation or experience alone). Decisions about ongoing coverage should be based on a combination of data from direct behavioral observation and measurement of progress on treatment objectives, as well as results of standardized assessments administered no more frequently than every six months *(strong recommendation).* Examples of standardized criterion-referenced and norm-referenced assessments include tests of adaptive functioning, developmental assessments, tests of cognitive skills, tests of communication skills, behavior checklists, and autism symptom rating scales.

> Rationale: Ensuring that patients are making meaningful progress is important to produce quality outcomes and effective use of resources. The six-month assessment period was chosen based on expert input to allow for sufficient time for progress while not being burdensome to providers and plans.

Focused ABA interventions are recommended for coverage to address specific target behaviors where comprehensive ABA has been determined not to be medically necessary, has been completed, or where there is objective evidence that it did not produce meaningful progress or prevent serious disability in the patient, or for treatment of a co-morbid condition. Treatment targets should include the core symptoms of ASD as well as associated behaviors and skills that directly affect the patient's health, safety, and overall functioning (e.g., self-injury, aggression, pica, elopement, self-care, cooperating with medical and dental procedures, communicating, seeking help appropriately, avoiding hazards). The intensity and duration of focused ABA interventions shall be determined by the ABA treatment team based on evidence of medical necessity and patient progress. Coverage is recommended for a minimum of 8 hours per month of direct behavior assessment, monitoring, staff and parent training, analysis and treatment planning, and clinical oversight by a professional behavior analyst and a minimum of 8 hours per week of behavior technician services. Additional hours may be authorized on an individual basis when medically necessary. The treatment team shall also prioritize treatment targets, ensuring that interventions to reduce problem behaviors are accompanied by interventions to increase functional alternative behaviors and skills. Focused ABA interventions may be delivered in inpatient or outpatient settings or a combination thereof *(strong recommendation).*

> Rationale: Systematic reviews of aggregated ABA controlled clinical trials, including meta-analyses, show that focused ABA interventions are more effective than no treatment, treatment as usual, and several other types of interventions for reducing problem behaviors and building useful skills, thereby promoting growth and development and preventing serious disability (thus meeting the American

Academy of Pediatrics criteria for medically necessary treatments). There is insufficient scientific evidence that interventions other than ABA meet those criteria, and clear evidence that failure to provide ABA treatment can result in severe disability. Focused ABA interventions are appropriate for many children and youths with ASD, including some who have completed comprehensive ABA treatment and are transitioning to typically available services. The recommendations are based on the best available scientific evidence as well as expert input and best practices in ABA treatment (see *Behavior Analyst Certification Board Guidelines: Health Plan Coverage of Applied Behavior Analysis Treatment for Autism Spectrum Disorders*).

Parent/caregiver involvement and training is recommended to be a component of comprehensive and focused ABA treatments *(strong recommendation).*

Rationale: Evidence and expert input indicated that parental involvement in ABA is a key part of effective treatment. Where parent capacity for involvement is limited, inpatient day treatment is recommended.

Behavior analytic assessment and analysis is recommended for coverage for an initial period of 40 hours to establish the medical necessity of either comprehensive or focused ABA treatment and to identify treatment targets.

Rationale: Behavior analytic services are recommended for an initial period to collect direct observational data on the patient's levels of functioning and severity of needs, evaluate current levels of services and supports, establish a baseline for evaluation of continued coverage, identify and prioritize treatment targets, and recommend medically necessary treatment procedures, settings, and intensity.

Individuals ages 13 and older

Comprehensive ABA interventions are recommended for coverage for treatment of autism spectrum disorder in persons over the age of 12 when there is a discrete set of clearly defined, medically important objectives for the treatment. (*strong recommendation*).

Rationale: There is a large body of ABA controlled clinical trials published in peer-reviewed scientific journals that involved several thousand older individuals with ASD and related disorders. Moreover, these studies have typically been conducted in settings where the interventions comprised multiple ABA procedures with a multiple treatment objectives. Further, there is no evidence that comprehensive ABA treatment is ineffective for producing clinically significant improvements in older patients, and there is even less evidence to support any alternative treatment

model for that population. Systematic reviews of that research, including meta-analyses, have demonstrated that many ABA interventions, singly and in various combinations, are more effective than no treatment, treatment as usual, and several other types of interventions for reducing problem behaviors and building useful alternative skills, thereby promoting growth and development and preventing serious disability in individuals with ASD over the age of 12 years (thus meeting the American Academy of Pediatrics criteria for medically necessary treatments). Decisions about the nature, intensity, and duration of ABA treatments for each patient with ASD over the age of 12 years should be based on objective evidence of the medical necessity of the treatment for that individual. Failure to treat autism can result in serious disability, making traditional randomized or other group-design clinical trials unreasonable as per the HERC Guidance Development Framework, and warranting a strong coverage recommendation even if evidence is deemed insufficient.

Focused ABA interventions are recommended for coverage to address specific target behaviors where comprehensive ABA has been determined not to be medically necessary, has been completed, or where there is objective evidence that it did not produce meaningful progress or prevent serious disability in the patient, or for treatment of a co-morbid condition. Treatment targets should include the core symptoms of ASD as well as associated behaviors and skills that directly affect the patient's health, safety, and overall functioning (e.g., self-injury, aggression, pica, elopement, self-care, cooperating with medical and dental procedures, communicating, seeking help appropriately, avoiding hazards). The intensity and duration of focused ABA interventions shall be determined by the ABA treatment team based on evidence of medical necessity and patient progress. Coverage is recommended for a minimum of 8 hours per month of direct behavior assessment, monitoring, staff and parent training, analysis and treatment planning, and clinical oversight by a professional behavior analyst and a minimum of 8 hours per week of behavior technician services. Additional hours may be authorized on an individual basis when medically necessary. The treatment team shall also prioritize treatment targets, ensuring that interventions to reduce problem behaviors are accompanied by interventions to increase functional alternative behaviors and skills. Focused ABA interventions may be delivered in inpatient or outpatient settings or a combination thereof *(strong recommendation)*.

Rationale: Systematic reviews of aggregated ABA controlled clinical trials, including meta-analyses, show that focused ABA interventions are more effective than no treatment, treatment as usual, and several other types of interventions for reducing problem behaviors and building useful skills, thereby promoting growth and development and preventing serious disability (thus meeting the American

Academy of Pediatrics criteria for medically necessary treatments). There is insufficient scientific evidence that interventions other than ABA meet those criteria, and clear evidence that failure to provide ABA treatment can result in severe disability. Focused ABA interventions are appropriate for many children and youths with ASD, including some who have completed comprehensive ABA treatment and are transitioning to typically available services. The recommendations are based on the best available scientific evidence as well as expert input and best practices in ABA treatment (see *Behavior Analyst Certification Board Guidelines: Health Plan Coverage of Applied Behavior Analysis Treatment for Autism Spectrum Disorders*).

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Inpatient ABA treatment is recommended where parent capacity for active involvement in treatment is limited, the risk to the client's health is significant (e.g., due to self injury, aggression, pica, elopement), or treatment is determined to be medically necessary to produce gains in skills such as self-care, cooperation with medical and dental procedures, functional communication, or personal safety. A decision to discharge the patient should be based upon treatment team determination that the client is behaviorally stable and no longer a risk to self or others when treatment is implemented by trained care providers, the treatment has been generalized and modified to the extent it can be implemented in community settings, and care providers have been trained to implement the ABA interventions correctly and consistently *(strong recommendation).*

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Health Care for Children Who Suffer from Autism: Maximizing the Value Returned from Health Care Coverage

Eric V. Larsson, Ph.D., L.P., B.C.B.A.-D. (2012)

The use of regulatory resources is most cost-effective when incorporating measures of quality and outcomes, as well as quantity. Applied Behavior Analysis for autism offers the kind of objective data needed to make efficient care determinations.

This focus mirrors concepts proposed by Health Care Reform initiatives, such as those by the Mayo Clinic and the Minnesota Department of Health's value-based initiative. These initiatives combine measures of cost with measures of quality to control health care delivery based upon value.

Where independent case reviewers can not hope to provide the level of oversight needed to make cost-saving determinations for each individual, a system of managing provider organizations can be much more efficient and effective.

Medical necessity should be based upon the evidence and the community standard of care. However, to date, most policy makers have only relied upon one level of evidence-based care determination. But actually, there are five important levels of value-based decision-making that result in the most helpful allocation of resources to all children.

Because Applied Behavior Analysis for autism incorporates objective outcome data, it is one area where all five levels of evidence that can be used to manage the costs of autism treatment. How would this work?

In brief, in 1972, Lovaas published the first long-range outcome study of early intervention with children with autism. For the first time, this study showed the potential that children had to make clinically important gains. These children had all been placed into state hospitals, with no hope of recovery from their symptoms, and no hope of acquiring basic language and play skills. To everyone's amazement, the 16 children did make clinically significant progress. But what is less well known is that the study was the first of its kind to identify prognostic indicators of response to treatment. Essentially, Lovaas was able to identify four types of candidates for treatment. These four types came from a matrix of older and younger children, interacting with children who had high parental involvement and low parental involvement. Lovaas' conclusions were that the children, who responded best, were the younger children, who had high parental involvement. He then initiated his plan to focus on that segment of the population. His determination was to provide the earliest possible treatment in the family homes of the children, with the plain intention of training the parents to be the children's own therapists.

The other children who did not benefit from parent training were not to be "thrown away," as they had already been by society, but instead they were to be referred to other valuable treatment modalities such as center-based treatment, with other services such as medical management, respite, and social groups.

In 1987 and 1993, his subsequent research proved the value of that approach, and found more accurate measures of responsiveness to treatment. When replications of the approach were published in 2005, 2006, and 2007, it became clear that we can maximize the value of our limited health care dollars by focusing on real outcome measures and determining the best matrix of services for each child.

Today, the present cost-containments system would incorporate these concepts to determine the absolutely best treatment options for each child, and make the best possible referrals, based upon their prognostic indicators. Each child will receive their optimal treatment, and society's resources will be best conserved, if each child can benefit from the earliest possible care determinations. But it is much more than a single decision. What we have learned in this dynamic, 35-year process of treatment development, is that there are several levels of evidence that help determine the best course of treatment for each child. See the following table for a summary of the process.

Using evidence-based treatment data to maximize the value of health care for each child

1) Scientific Actuarial Research on Average Costs and Outcomes

The first level is the obvious one that most policy makers are aware of: the research on evidence-based treatment – children should receive the kind and level of treatment that has been proven to be most effective in meeting clinical needs. This evaluation must be ongoing, as new research indicates innovative approaches.

2) Process Research on Service-Delivery Effectiveness and Accessibility

But, the second level is to determine the best service-delivery method for each treatment. Some methods of delivery will be much more effective than will others. Some will be much less costly than others. Some will entail much less risk than others. And some will be much more accessible than other.

At this level the important principle of "payment reform," is investigated. Some models of payment create disincentives for cost-effectiveness. For example, if payment is only made for the direct hours of one-to-one behavior therapy, and not for the behavior assessment, behavior analysis, and clinical supervision, then there is a disincentive to phase out intensity as the child responds, because a certain intensity of direct hours is required in order to cover the overhead costs. There is also a disincentive to provide low-intensity parent training to less affected children. The reimbursement model may also not accommodate long-distance services in rural areas. Or it may not allow for high-risk services for the dangerous children who become the highest cost children in the future.

3) Value-Based Assessment and Certification of Individual Provider Agencies

However, the third level of care determination is based upon a frank realization that some provider agencies are better suited to success with certain forms of treatment than others. And some have frankly abused the system. Therefore this level of care determination is to identify the most cost-effective provider organizations that are delivering each type of treatment.

4) Prescriptive Assessment of Individual Children at Intake

A fourth level is to identify the optimal form of treatment, intensity, and service delivery for each individual child at intake – to prescribe this optimal treatment based upon individual measures of prognosis, such as parental involvement, age, and complicating conditions.

5) Prescriptive Assessment of Individual Children's Responsiveness to Treatment

But the maximum value is not received until the fifth level in which care-determination is based upon each individual child's responsiveness to treatment. Each child should be periodically re-assessed and referred to the optimal treatment as they show individualized patterns of response to treatment, just as every other form of medicine does. Each child will not respond the same way, and present technology does not accurately predict treatment outcomes three years hence. In our ongoing research we have found that a dynamic assessment of a child's response to treatment over time is a much better predictor than is a single static assessment at a single point in time. Therefore, in the case of early intensive home-based intervention, we have found that every six months is a cost-effective time frame for re-evaluating responsiveness to treatment and making different referrals based upon these assessments.

What Will be the Cost Impact of Covering ABA for autism?

Several state Medicaid programs and private insurance companies have had a formal ABA benefit for 6 or more years, and have published data on the actual cost of their autism coverage. With that kind of substantial track record, here's what we do know for a fact.

In states who have provided accessible funding and ABA services over a period of years, the actual utilization of ABA has proven to be much less than expected. Some of the reasons for the lower utilization of ABA include:

1) While the number of cases of autism that are diagnosed are very high, only about one third of the children have high needs for care.
2) The average age of diagnosis is estimated by the CDC to be 5.7 years of age (Shattuck, et. al., 2009). While the intent of ABA is to be delivered as early as possible, half of the target pool is not identified until after reaching school age. This dramatically decreases the average weekly hours of home-based services.
3) Not every family will be able to access ABA due to their location and other family challenges. The rural and the inner city families continue to be dramatically underserved.
4) Many other kinds of treatments are available, and various families will make other value-based choices than to engage in intensive services.
5) It continues to be a significant challenge to train the medical and social service referral sources to understand and refer to ABA.
6) The growth in available providers has been slower than might be expected, due to the high cost of personnel training and certification.

Therefore the average cost of ABA per child with autism is much lower than commonly estimated. Here are four state's experiences:

The state of Pennsylvania's Medicaid program has been widely available to children with autism since the mid 1990's. Abt Associates Inc (2007) reported that the Pennsylvania Medicaid program covered 13,800 children with autism in 2007, at an average annual cost of $14,300 per child for all services (including ABA). There were 8,516 other diagnosed children with autism who did not access services. If this cost was extended to all children with autism (both covered and not covered), the average cost was $8,843 per child. If this cost was extended to all children in Pennsylvania, the cost was $59 per child.

The state of Wisconsin also had widely available services since the mid 1990's. In 2004, they reported that after six years of widespread availability of Medicaid funding for ABA, only 1,073 children, out of 7,867 eligible children, were accessing ABA in 2002. The average cost per child accessing ABA was $29,545. The average cost per eligible child was $4,030. The average cost per every child was $27 per year.

In Minnesota, after seven years of widely accessible Medicaid funding, it was reported in 2009 that only 541 children out of a total of 3,333 eligible children, were accessing ABA. The average cost of treatment for those children was $31,000. If that cost were averaged across all children with autism, the average cost would be $2,910. Across all children in the state, that cost would be $19 per child per year. At the same time Blue Cross Blue Shield of Minnesota also made coverage of EIBI widely available. Their data closely matches the incidence and cost data of the Medicaid program.

Similarly, in one of the Medicaid regions of California where ABA has been most widely available over a period of years, it was reported in 2009 that that about one third of the eligible children accessed ABA. The average cost was slightly over $10,000 per child treated. Across all of the children with autism in the region, the cost was $3,361 per child, and across all children in the region, the cost was $22 per child per year.

In these four states, the average utilization of ABA was 34% of all eligible children. The average cost per child (all children in the state or region) was $32 per year.

References

Research on Intensive Early Intervention

Cohen, H., Amerine-Dickens, M., & Smith, T., (2006). Early Intensive Behavioral Treatment: Replication of the UCLA Model in a Community Setting. *Developmental and Behavioral Pediatrics*, 27, S145-S155.

Eikeseth, S., Smith, T., Jahr, E., & Eldevik, S. (2007) Outcome for Children with Autism who began Intensive Behavioral Treatment Between Ages 4 and 7: A Comparison Controlled Study. *Behavior Modification*, 31, 264-278.

Lovaas, O.I. (1987). Behavioral treatment and normal educational and intellectual functioning in young autistic children. *Journal of Consulting and Clinical Psychology*. *55*, 3-9.

Lovaas, O.I., Koegel, R., Simmons, J.Q., & Long, J.S. (1973). Some generalization and follow-up measures on autistic children in behavior therapy. *Journal of Applied Behavior Analysis*. *6*, 131-166.

McEachin, J.J., Smith, T., & Lovaas, O.I. (1993). Long-term outcome for children with autism who received early intensive behavioral treatment. *American Journal on Mental Retardation*. *97,* 359-372.

Sallows, G.O., & Graupner, T.D. (2005). Intensive Behavioral Treatment for Children With Autism: Four-Year Outcome and Predictors. *American Journal on Mental Retardation*, 110, 417-438.

Research on the Cost Effectiveness of Intensive Early Intervention

Bouder, J.N., Spielman, S., & Mandell, D.S. (2009). Brief report: Quantifying the impact of autism coverage on private insurance premiums. *Journal of Autism and Developmental Disorders.* Published online February 13, 2009, DOI 10.1007/s10803-009-0701-z.

California Legislative Blue Ribbon Commission on Autism (2007). *Report: An Opportunity to Achieve Real Change for Californians with Autism Spectrum Disorders.* Sacramento, CA: The Legislative Office Building (HTTP://senweb03.sen.ca.gov/autism).

Chasson, G.S., Harris, G.E., & Neely, W.J. (2007). Cost comparison of early intensive behavioral intervention and special education for children with autism. *Journal of Child and Family Studies.* 16, 401-413.

Green, C., Bassett, K., & Kazanjian, A. (2000). *Critical appraisal of submitted cost-benefit models of 'Lovaas' early intensive behavioural intervention for autism.* Vancouver, BC: BC Office of Health Technology Assessment.

Jacobson, J. & Mulick, J., (2000). System and cost research issues in treatments for people with autistic disorders. *Journal of Autism & Developmental Disorders*, 30, 585–593.

Jacobson, J.W., Mulick, J.A., & Green, G. (1998). Cost benefit estimates for early intensive behavioral intervention for young children with autism - general model and single state case. *Behavioral Interventions*, 13, 201-226.

Motiwala, S.S., Gupta, S., & Lilly, M.D. (2006). The cost-effectiveness of expanding intensive behavioural intervention to all autistic children in Ontario. *Healthcare Policy*, 1, 135-151.

Mulick, J.A., Jacobson, J.W., & Shreck, K.A. (1999, September). *Class and comorbidity in early intensive behavioral treatment of autism: The case for mainstreaming a cottage industry*. Presented at the 2nd European Conference on Mental Health in Mental Retardation, London, UK.

National Research Council (2001). *Educating Children with Autism,* Committee on Educational Interventions for Children with Autism, Division of Behavioral and Social Sciences and Education, Washington, D.C.: National Academy Press.

Rolnick, A., & Grunewald, R. (2003, December). Early childhood development: Economic development with a high public return. *Fedgazette,* December, 6-12.

Shattuck, P.T., et al. (2009). Timing of Identification Among Children With an Autism Spectrum Disorder: Findings From a Population-Based Surveillance Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48, 474-483

Sherman, J., Barker, P., Lorimer, P., Swinson, R., & Factor, D. (1988). Treatment of autistic children: Relative effectiveness of residential, out-patient and home-based interventions. *Child Psychiatry and Human Development,* 19, 109-125.

Simmermon, L. (2000, April). Autism costs in Canada. Downloaded from: http://www.autismtoday.com/articles/Autism_Costs_In_Canada.htm on October 16, 2008.

Shonkoff, J.P. & Hauser-Cram, P. (1980). Early Intervention for Disabled Infants and Their Families: A Quantitative Analysis. *Pediatrics,* 80, 650-658.

Wood, M.E. (1981). Costs of Intervention Programs. In C. Garland and others, eds., *Early Intervention For Children With Special Needs And Their Families: Findings And Recommendations*. Westar Series Paper No. 11. Seattle, WA: University of Washington, 207-278.

Research on the Costs of Autism and Related Disorders

Alba, K., Prouty, R., Scott, N., & Lakin, K.C. (2008). Changes in Populations of Residential Settings for Persons With Intellectual and Developmental Disabilities Over a 30-Year Period, 1977–2007. *Intellectual and Developmental Disabilities.* 46, 257-260.

Bebbington, A., & Beecham, J. (2007). Social services support and expenditure for children with autism. *Autism.* 11, 43-61.

Braddock, D., Hemp, R., & Rizzolo, M.C. (2004). State of the States in Developmental Disabilities: 2004. *Mental Retardation.* 42, 356-370.

Centers for Disease Control and Prevention (2007). *Prevalence of the Autism Spectrum Disorders (ASDs) in Multiple Ares of the United States, 2000, 2002. Community Report from the Autism and Developmental Disabilities Monitoring (ADDM) Network.* Atlanta, GA: Centers for Disease Control and Prevention.

Croen, L.A., Najjar, D.V., Ray, G.T., Lotspeich, L., & Bernal, P. (2006). A comparison of health care utilization and costs of children with and without autism spectrum disorders in a large group-model health plan. *Pediatrics.* 118, e1203-e1211.

Davies, K. (2005). *Economic Costs of Diseases and Disabilities Attributable to Environmental Contaminants in Washington State.* Seattle, WA: Collaborative for Health and Environment – Washington Research and Information Working Group.

Ganz, M.L. (2007). The lifetime distribution of the incremental societal costs of autism. *Archives of Pediatric and Adolescent Medicine*, 161, 343-349.

Gurney, J.G., McPheeters, M.L., & Davis, M.M. (2006). Parental report of health conditions and health care use among children with and without Autism: National survey of children's health. *Archives of Pediatric and Adolescent Medicine*, 160. 825-830.

Hackenmiller-Paradis, R. (2008). *The Price of Pollution: Cost Estimates of Environmentally-Related Disease in Oregon.* Portland, OR: Oregon Environmental Council.

Honeycutt, A., Dunlap, L., Chen, H., al Homsi, G., Grosse, S., & Schendel, D. (2004). Economic Costs associated with Mental Retardation, Cerebral Palsy, Hearing Loss, and Vision Impairment – United States 2003. *Morbidity and Mortality Weekly Report.* 53, *Atlanta*, GA: Centers for Disease Control., 57-59.

Jackson, M., Vos, J., Jacobson, D., Zimmer, A., & Dandelake, L. (1997). *Special Education*. St. Paul, MN: Program Evaluation Division, Office of the Legislative Auditor.

Jarbrink, K, & Knapp, M. (2001). The economic impact of autism in Britain. *Autism*, 5, 7–22.

Jarbrink, K., McCrone, P., Fombonne, E., Zanden, H., & Knapp, M. (2007). Cost-impact of young adults with high-functioning autistic spectrum disorder. *Research in Developmental Disabilities.* 28, 94-104.

Kielinen, M., Rantala, H., Timonen, E., Linna, S.L., & Moilanen, I. (2004). Associated medical disorders and disabilities in children with autistic disorder: A population-based study. *Autism*, 8, 39-48.

Kogan, M.D., Strickland, B.B., Blumberg, S.J., Singh, G.K., Perrin, J.M., & van Dyck, P.C. (2008). A National Profile of the Health Care Experiences and Family Impact of Autism Spectrum Disorder Among Children in the United States, 2005-2006. *Pediatrics*. E1149-e1158.

Kooistra, W. (November 15, 2007). *Mental Health Transformation in Minnesota.* Presentation to the Nebraska Department of Health and Human Services State Strategic Partnership Session, Aurora, NE. (retrieved from http://www.hhs.state.ne.us/Behavioral_Health/SSPS/Kooistra-Presentation.pdf on May 4, 2008).

Krauss, M. W., Gulley, S., Sciegaj, M., & Wells, N. (2003). Access to specialty medical care for children with mental retardation, autism, and other special health care needs. *Mental Retardation*, 41, 329–339.

Lakin, K.C., Doljanac, R., Byun, S., Stancliffe, R.J., Taub, S., & Chiri, G. (2008). Factors Associated With Expenditures for Medicaid Home and Community Based Services (HCBS) and Intermediate Care Facilities for Persons With Mental Retardation (ICF/MR) Services for Persons With Intellectual and Developmental Disabilities. *Intellectual and Developmental Disabilities.* 46, 200-214.

Lakin, K.C., Prouty, R., & Alba, K. (2007). Medicaid Institutional and Home and Community-Based Services Expenditures for Persons With ID/DD Within the Overall Medicaid Program. *Intellectual and Developmental Disabilities.* 45, 418-421.

Lakin, K.C., Prouty, R., Alba, K., & Scott, N. (2008). Twenty-Five Years of Medicaid Home and Community Based Services (HCBS): Significant Milestones Reached in 2007. *Intellectual and Developmental Disabilities.* 46, 325-328.

Lakin, K.C., Prouty, R., & Coucouvanis, K. (2007). HCBS Recipients are increasingly likely to live with parents and other relatives. *Intellectual and Developmental Disabilities.* 45, 359-361.

Larson, S.A., Scott, N., & Lakin, K.C. (2008). Changes in the Number of People With Intellectual or Developmental Disabilities Living in Homes They Own or Rent Between 1998 and 2007. *Intellectual and Developmental Disabilities.* 46, 487-491.

Maltby, J. (2000). The cost of autism: more than meets the eye. *Advocate.* Bethesda, MD: Autism Society of America, 12-16.

Mandell, D. S., Cao, J., Ittenbach, R., & Pinto- Martin, J. (2006). Medicaid expenditures for children with autistic spectrum disorders: 1994 to 1999. *Journal of Autism and Developmental Disorders*, 36, 475–485.

Myers, S.M., Johnson, C.P. & the American Academy of Pediatrics Council on Children With Disabilities, (2007). Management of children with autism spectrum disorders. *Pediatrics*. 120, 1162–1182. Available online at http://aappolicy.aappublications.org/cgi/reprint/pediatrics;120/5/1162.pdf.

Ming, X., Brimacombe, M., Chaaban, J., Zimmerman-Bier, B., & Wagner, G.C. (2008). Autism spectrum disorders: Concurrent clinical disorders. *Journal of Child Neurology.* 23, 6-13.

Minnesota Department of Human Services (2004). *New Cost of Care Rates as of July 1, 2004.* Bulletin 04-77-01.

Montes, G. & Halterman, J.S. (2008). Child care problems and employment among families with preschool-aged children with autism in the United States. *Pediatrics*, 122, e202-e208.

Newacheck, P.W. & Kim, S.E. (2005). A national profile of health care utilization and expenditures for children with special health care needs. *Archives of Pediatric and Adolescent Medicine*, 159, 10-17.

Newschaffer, C.J., et al. (2007). The epidemiology of autism spectrum disorders. *Annual Review of Public Health.* 28, 21.1-21.24.

Prouty, R., Alba, K.M., Scott, N.L., Lakin, K.C. (2008). Where People Lived While Receiving Services and Supports From State Developmental Disabilities Programs in 2006. *Intellectual and Developmental Disabilities.* 46, 82-85.

Prouty, R.W., Smith, G., & Lakin, K.C. (eds.) (2005). *Residential Services for Persons with Developmental Disabilities: Status and Trends Through 2004.* Minneapolis: University of Minnesota, Research and Training Center on Community Living.

Ray, G.T., Levine, P., Croen, L.A., Bokhari, F.A.S., Hu, T., & Habel, L.A. (2006). Attention-Deficit/Hyperactivity Disorder in children: Excess costs before and after initial diagnosis and treatment cost differences by ethnicity. *Archives of Pediatric and Adolescent Medicine.* 160, 1063-1069.

Ruble, L. A., Heflinger, C. A., Renfrew, J. W., & Saunders, R. C. (2005). Access and service use by children with autism spectrum disorders in Medicaid managed care. *Journal of Autism and Developmental Disorders*, 35, 3–13.

Stancliffe, R.J., & Lakin, K.C. (2004). *Policy Research Brief: Costs and Outcomes of Community Services for Persons with Intellectual and Developmental Disabilities*. Minneapolis: University of Minnesota, Research and Training Center on Community Living.

Transande, L., Landrigan, P.J., & Schechter, C. (2005). Public Health and economic consequences of methyl mercury toxicity to the developing brain. *Environmental Health Perspectives.* 113, 590-596.

Tschida, J., (2005). Costs, Options, and Inclusion: Issues in Health Care for People with Disabilities. In Gaylord, V., Abery, B., Cady, R., Simunds, E., & Palsbo, S. (Eds.). *Impact: Feature Issue on Enhancing Quality and Coordination of Health Care for Persons with Chronic Illness and/or Disabilities*, 18, Minneapolis: University of Minnesota: Institute on Community Integration.

United States Government Accounting Office (2005). *Special Education: Children with Autism*. Report to the Chairman and Ranking Minority Member, Subcommittee on Human Rights and Wellness, Committee on Government Reform, House of Representatives. Washington DC: GAO.

Young, A., Ruble, L., & McGrew, J. (2009). Public vs. private insurance: Cost, use, accessibility, and outcomes of services for children with autism spectrum disorders. *Research in Autism Spectrum Disorders.* 3, 1023-1033. oi:10.1016/j.rasd.2009.06.006

Research on the Costs of Insurance for Autism

Abt Associates Inc. (2008). *Autism Spectrum Disorders Mandated Benefits Review Panel Report: Evidence Submitted Concerning Pennsylvania HB 1150.* Durham NC: Abt Associates Inc.

Avner, M., & Halleland, K. (2001). *Meeting Every Child's Mental Health Needs: A Public Priority – Final Report of the Citizen's League Committee on Children's Mental Health.* St. Paul, MN: Citizen's League.

Bouder, J.N. (2007). *In Response to the Notice in re Mandated Benefits Pertaining to HB 1150 of 2007*. Hershey, PA: Vista Foundation. pp. 1-17 and Exhibits A-E.

Bunce, V.C., Wieske, J.P., & Prikazsky, V. (2007). *Health Insurance Mandates in the States 2007.* Alexandria VA: The Council for Affordable Health Insurance.

Chan, B., & Vanderburg, N., (1999). Medicaid TEFRA Option in Minnesota: Implications for patient rights. *Health Care Financing Review,* 21. 65-78.

Coalition for Healthy Communities (2006). *Failure to Enact Mental Health Parity: Consequences for Ohio Businesses and Communities.* Columbus, OH: Coalition for Health Communities.

Fuhr, J.P. (2007). The impact of health benefit mandates: The California review program. *Health Watch*. 20-21.

Hatch, M. (2004). *Health Care: Making the Best of a Bad Bargain.* St. Paul, MN: Office of Attorney General.

Ireys, H.T., Pires, S., & Lee, M. (2006). *Public Financing of Home and Community Services for Children and Youth with Serious Emotional Disturbances: Selected State Strategies.* Washington DC: Office of Disability, Aging and Long-Term Care Policy, US. Department of Health and Human Services.

Leslie, D., & Martin, A. (2007). Health care expenditures associated with autism spectrum disorders. *Archives of Pediatrics & Adolescent Medicine*, 161(4), 350–355. doi:10.1001/archpedi. 161.4.350.

Long, E., Jacobson, D., & Frazier, A. (2001). Insurance for Behavioral Health Care. St. Paul, MN: Program Evaluation Division, Office of the Legislative Auditor.

Minnesota Department of Health (2008). *Administrative Costs at Minnesota Health Plans in 2006.* St. Paul, MN: Health Economics Program, Minnesota Department of Health.

Minnesota Departments of Human Services, Employee Relations, Health, and Commerce. (2007). *Health Care Payment System Reform in Minnesota.* St. Paul, MN: Minnesota Departments of Human Services, Employee Relations, Health, and Commerce.

Minnesota Mental Health Action Group (2005). *Road Map for Mental Health System Reform in Minnesota.* St. Paul, MN: Citizen's League.

Minnesota Ombudsman (1999). *Why Do We Wait? A Mental Health Report.* St. Paul, MN: Office Of The Ombudsman For Mental Health And Mental Retardation.

Satcher, D. (1999). *Chapter 6: Organizing and Financing Mental Health Services. In Mental health: A report of the surgeon general*. Bethesda, MD: U.S. Public Health Service.

Wieske, J.P. (2007). *2007 State Legislator's Guide to Health Insurance Solutions.* Alexandria VA: The Council for Affordable Health Insurance.

Research on the Costs of Health Care

Baicker, K., & Chandra, A. (2004). Medicare spending, the physician workforce, and beneficiaries' quality of care. *Health Affairs.* (retrieved from http://content.healthaffairs.org/cgi/reprint/hlthaff.w4.184v1 on May 4, 2008).

Bailey, K., & Wikler, B. (2007). *Too Great a Burden: Minnesota's Families at Risk.* Washington, DC: Families USA.

Bleiden, N., Flinders, S., Hawkins, K., Reid, M., Alphs, L.D., & Arfken, C.L. (1998). Health status and health care costs for publicly funded patients with schizophrenia started on clozapine. *Psychiatric Services.* 49, 1590-1593.

Center for the Evaluative Clinical Sciences (2006). *The Care of Patients with Severe Chronic Illness: A Report on the Medicare Program by the Dartmouth Atlas Project.* Hanover, NH: Dartmouth Atlas Project.

Conover, C.J. (2004). Health care regulation: A $169 billion hidden tax. *Policy Analysis*, 527. Washington, DC: Cato Institute.

Goldman, D.P. & McGlynn, E.A. (2005). *U.S. Health Care: Facts about Cost, Access, and Quality.* Santa Monica, CA: RAND Corporation.

Gorsky, R.D., & Teutsch, S.M. (1995). Assessing the effectiveness of disease and injury prevention programs: Costs and consequences. *Morbidity and Mortality Weekly Report.* 44, Atlanta, GA: Centers for Disease Control.

National Coalition on Health Care (2008). *Health Insurance Cost: Facts on the Cost of Health Care.* (Retrieved from http://www.nchc.org/facts/cost.shtml on February 22, 2008).

Yunker, J., Walstrom, T., & Feige, D. (1995). *Health Care Administrative Costs*. St. Paul, MN: Program Evaluation Division, Office of the Legislative Auditor.

Value-Based Reimbursement for Health Care

Chorpita, B. F., & Daleiden, E. L. (2003). Building evidence-based systems in children's mental health. In A. E. Kazdin and J. R. Weisz (Eds.) *Evidence-Based Psychotherapies for Children and Adolescents*. New York: Oxford.

Cortese, D.A., & Korsmo, J.O. (2009). Putting U.S. health care on the right track. *The New England Journal of Medicine*, 361, 1326-1327.

Hermann, R.C., Chan, J.A., Zazzali, J.L., & Lerner, D. (2006). Aligning measurement-based quality improvement with implementation of evidence-based practices. *Administration and Policy in Mental Health and Mental Health Services Research.* 33, 636-645.

Palinkas, L. A., Schoenwald, S. K., Hoagwood, K. E., Landsverk, J., Chorpita, B. F., Weisz, J. R., & the Research Network on Youth Mental Health. (2008). An ethnographic study of implementation of evidence-based practice in child mental health: First steps. *Psychiatric Services*, 59, 738-746.

Porter, M.E. (2009). A strategy for health care reform: Toward a value-based system. *The New England Journal of Medicine.* 361, 109-112.

Smoldt, R.K., & Cortese, D.A. (2007). Pay-for-performance or pay for value? *Mayo Clinic Proceedings,* 82, 210-213.

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How should the intensity of BCBA Supervision and BT Intervention be managed for Applied Behavior Analysis (ABA) and Early Intensive Behavioral Intervention (EIBI) for Autism?

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Summary.

Early Intensive Behavioral Intervention (EIBI) is commonly described by the number of hours of staff time devoted to child training, commonly 35-40 hours per week in its intensive phases (though the reported range is 10-60 hours per week- see below). However, this characterization ignores the crucial medically necessary roles of the Behavior Analyst (BCBA) Clinical Supervisors and Senior (BCaBA) Behavior Therapist, who are critical to effective early intervention. Indeed, it is their experienced, direct role in therapy (in designing and dynamically adjusting therapy across the three-year sequence; training staff and parents on the ever-changing treatment procedures; and ensuring that the child's essential behavioral challenges are being remediated by both parents and staff), that is more essential than are the number of hours of direct time provided to the child by the rest of the behavior therapists. In many respects, the intensive direct time with the child is necessary to deliver sufficiently skilled therapy to every child treated, and to spell the parents of the incredible stress of round-the-clock functional therapy. But it is the skilled and timely direct Behavior Analysis that ensures that the child's therapy is not squandered. What follows is a review of the purpose of Behavior Analyst Clinical Supervision, and a review of the published evidence for Behavior Analyst Clinical Supervision and BCaBA Behavior Therapy services. In this review, the evidence supports a common range of 6-18 hours per week of such direct services (though the reported range is 2-22 hours per week). The most cost effective formula for hours is more complex than a simple average, as is shown below.

ABA research suggests ways to increase cost effectiveness and accessibility, and conforms with the trend in health care reform, which is to manage payment principles to motivate performance based upon outcomes, while avoiding disincentives for cost containment.

The net benefit of payment reform is that children will receive a more accurate level of intensity, customized to their needs. Their services will be more cost effective; they will be able to access treatment more quickly thus benefiting to a greater extent from earlier intervention; and the children who aren't benefitting will be determined more quickly and referred to better services as soon as possible.

The purpose of intensive Behavior Analyst Clinical Supervision and Behavior Therapy.

As certified by the Behavior Analyst Certification Board, ABA clinical supervisors have the credential of "Board Certified Behavior Analyst" – BCBA, and ABA senior behavior therapists have the credential of "Board Certified Assistant Behavior Analyst" – BCaBA.

The main roles of the BCBA and BCaBA include intensive parent training, periodic and accountable behavioral assessment of treatment, co-therapy interventions, and assurance of protection from harm.

Intensive parent training. One goal of Early Intensive Behavioral Intervention (EIBI), which most parents expressly seek, is to recover the child from the symptoms of autism (Maurice, 2001). One proven model of recovery-oriented treatment requires extensive parent involvement in a complex and dynamically changing treatment plan over a period of time that ranges from 18 months to five years for most cases (Lovaas & Smith, 2003). When providers do not share such goals, it is reasonable for them to gain the parents' consent for eclectic or lesser intensity services. But parents should be well informed that it also clearly proven in research that services which do not demand of the parents that they engage in effective therapeutic skills 24 hours a day, seven days a week, are unlikely to result in the kind of recovery that they should expect from the expense of intensive treatment (Leaf, Taubman, & McEachin, 2008).

The most central focus of this comprehensive therapy is the family therapy. In each family's case, extensive support and parent training is required, not just to train the parents to rationally use therapy skills, but also to support them in emotionally adopting new parenting behavior (which is in direct conflict with their history of parenting and long-term family history). Helping a parent to effectively follow through with therapy at the checkout counter, in the car, at the doctor's office, at mealtime, during a play date, at bedtime, at the grandparents' party, etc. is extremely challenging. In effective EIBI, the parents are not just responding effectively to a tantrum or other dangerous behavior, but they are also teaching social language skills at the same time, in embarrassing public situations. Further, the mother and father are not typically working together consistently when therapy begins, and their own conflicts must be addressed. Most typical families muddle through such difficult times and their children develop typically, because they are not afflicted by autism. However, if the goal of treatment is to change the very autistic symptoms that stand in the child's way of typical functioning, then families cannot succeed without extensive emotional support and skill-training expertise.

Parents do not change their emotional behavior easily. They require frequent direct supervision by sophisticated staff, during every aspect of therapy, in order to effect change. In addition, they require frequent parent-training co-therapy with a BCaBA behavior therapist who is narrating and instructing them while they observe the model of a behavior therapist working effectively with their child. In many cases, they also require separate direct counseling by the supervisors while a behavior therapist is managing their child, simply to be able to focus on the issues at hand without constant distractions.

As part of this extensive and necessary comprehensive family skills training, the provider would also conduct a weekly review with the parents and all staff involved. This clinical review "meeting" is essential to the continuity of care of the treatment plan, by providing simultaneous direction to the parents as well as the staff, and much specific family skills training is done in this "meeting" every week. Finally, this meeting serves as an ITP review meeting on a weekly basis to ensure that the family is fully and genuinely informed of the latest treatment recommendations, goals, and procedures. Their successful training in the meeting is part of their weekly consent to the treatment.

Periodic and accountable behavioral assessment of treatment. This heavy investment in comprehensive family therapy will be beneficial, to whatever extent the child achieves the recovery objectives. Should the child begin to show diminished results in this treatment, it is essential to be certain to detect that trend as quickly as possible, and attempt to remediate that; but also to be quick to transition the child on to traditional services if the intensive services can do no better. If treatment falls short of recovery goals, then at the very least, the parents will have been trained to effectively provide the ongoing treatment that the intensive provider will no longer provide. If treatment data shows that the child is maximally benefiting from the level of services provided, then the provider will continue to recommend the medically necessary level of services. The determination of medical necessity can be based upon the following process.

The EIBI provider develops, implements, and evaluates many specific individualized treatment objectives on a weekly basis. However, those weekly ITP objectives are not suitable for determining the ultimate prognosis or cost-benefit analysis of the child's treatment. Nor is it appropriate to expect either the family

or the funder to wait 18 months to five years in order to evaluate the results. Therefore, every six months the provider would conduct a comprehensive, multi-modal assessment, which includes an analysis of the child's functional behavior patterns, typical social behavior with the parents, clinical focus of therapy, criterion-referenced progress in a standard set of skills, norm-referenced progress on developmental milestones, independently evaluated progress on standardized assessments, overall rate of acquisition on weekly objectives, timely achievement of individualized benchmarks, treatment condition suitability, diagnostic status, and achievement of standard long-term discharge objectives. Then the provider would make recommendations to the family for the most suitable treatment services for the next six-month term. As part of this comprehensive assessment, the provider would evaluate the child's timely achievement of individualized benchmarks. In the child's case, the provider reports the results of such a multi-modal assessment and the subsequent determination of medical necessity for the next six months, with requests for prior authorization of coverage for treatment.

The Behavior Analyst Clinical Supervisors are heavily engaged in timely, direct observation, assessment, and treatment planning in order to ensure that the treatment is effective. Most of this activity is conducted at the same time as the behavior therapists work with the children. This is because the clinical supervisors must observe and intervene with staff and parent implementation on a weekly basis, in order to direct optimal treatment. The effectiveness of the clinical supervision is significantly weakened without direct observation, and active analysis of the effects of the clinical direction.

Then, every six months the clinical supervisor conducts a comprehensive, multi-modal assessment, which includes an analysis of the child's functional behavior patterns, typical social behavior with the parents, clinical focus, criterion-referenced progress in the standard set of skills, norm-referenced progress on developmental milestones, independently evaluated progress on standardized assessments, overall rate of acquisition on weekly objectives, timely achievement of individualized benchmarks, treatment condition suitability, diagnostic status, and achievement of standard ultimate discharge objectives.

Co-Therapy Interventions. In addition to the direct treatment of the parents, and the direct behavioral assessment and analysis functions of clinical supervision, EIBI is optimally composed of regular co-therapy interventions. Some particular examples of staff co-therapy activities are the following.

One of the most crucial skills, which leads to recovery from autism, is observational learning. The child who suffers from autism is simply not imitating the behavior of his siblings and peers with the natural fervor of the typical child. By contrast, the typical child readily seeks out other children, insightfully recognizes the intent of their behavior, and learns by imitating it. For example, imagine children playing tag in the back yard. A typical child may get a few pointers from their peers, but they quickly acquire the skill and all of its nuances. However for the child who is suffering with autism, the game is a confusing chaos, that they may not seem motivated to decipher. If the child becomes confused and fails, the child will lose motivation to participate. Therefore, in intensive intervention, the staff will simulate the complex peer activity in a less complex manner, and repeat the training until the child master's the skill. It will require the assistance of several persons (parents, siblings, peers, and/or staff) to successfully teach the observational learning.

In the first few months of treatment, as a necessary prerequisite to complex observational learning, one therapist will model simple play behaviors, while a second therapist immediately prompts and reinforces the child's imitation. If this therapy is efficient enough, the child will rapidly acquire the skill of imitation, and be on the road to substantial improvement. Without efficient therapy, children may fail to ever master such essential skills. Such co-therapy hours are provided by staff trainees, the BCaBA behavior therapist, two behavior therapists working together, and the therapists and parents working together.

In addition to essential therapy activities, there are many interventions that periodically require co-therapy hours simply in order to be practical. For example, picture the mother with four children. Her child, who suffers from autism, has extremely disruptive car behavior – unbuckling his seat belt and attempting to open the car door in transit, as well as biting at his siblings. To remediate this challenge, a single behavior therapist could repeatedly accompany the mother on car trips to establish a schedule of effective reinforcement, but because the mother has to care for her other children, she cannot participate in the intensity necessary to efficiently master this skill. A single therapist could attempt to provide

community outings to establish behavioral control, but would be distracted by the demands of safe driving. Instead the most efficient, practical solution is to have two therapists travel together. One provides the demanding schedule of musical and edible reinforcement, while the second drives. On occasion, the BCaBA behavior therapist will accompany the staff on such a trip, in order to model the currently recommended procedure or give feedback on effective timing of reinforcement and prompts.

Protection from Harm. While the above reasons for adequate supervision are most directly related to cost effectiveness, one essential reason for adequate supervision is safety. Without adequate clinical oversight, bachelor's level staff cannot be expected to automatically anticipate risks, perform procedures in a safe manner, and use the necessary levels of vigilance for danger. For example, many of the activity reinforcers entail risks to the child. Children jump on trampolines, which carry high risks for physical injury. Children swim in pools and at the beach, which carry risks for drowning. Children are attracted to dangerous items such as matches and lawn mowers. Children climb dangerously. Children bolt in the community. Further, when physical guidance is employed, the risks of injury from inappropriate guidance are present. It is only the experienced supervisor who can be counted on to observe a potentially risky situation, anticipate the risks, short-circuit dangerous activities, and train and motivate the necessary vigilance to keep children safe. They must be given the support necessary to afford this essential supervision.

In summary, it is the experienced and skilled Behavior Analyst Clinical Supervisors and BCaBA Behavior Therapists who evaluate the child's medical needs; develop the individualized treatment program; prescriptively evaluate the child's ongoing response to treatment; train parents, staff, and community members in timely implementation of progressively more complex programming; ensure continuity of care among team members; and conduct thorough periodic assessments to ensure accountability. In contrast, the one-to-one behavior therapists average only about one year of experience and are unable to make the timely cost effective analyses and improvements to children's programming. In short, it is the clinical supervisor's role that enables the treatment to be rehabilitative and time-limited, and thus cost-effective. While it is conceivable that a Ph.D. or other licensed professional could deliver these services, it is unlikely to be cost effective with customary fee structures; and the EIBI service is unlikely to be accessible to large numbers of families, when these roles are filled by professionals at this level. Instead the following research establishes the suitability of master's and bachelor's level Behavior Analysts and BCaBA Behavior Therapists in fulfilling these roles.

To be cost-effective, we have found that the clinical supervision is best split between three roles: A Behavior Analyst Clinical Supervisor who has the training and credentials of a master's level Board Certified Behavior Analyst, has five years of experience in an intensive early intervention behavior therapy program, and has passed the competencies to supervise an intensive home-based program for autism. This person provides up to 350 hours of direct supervision to the individual family's treatment program per year. This Behavior Analyst Clinical Supervisor then delegates much of the extensive case-management and staff and parent training to a BCaBA Behavior Therapist, who has at least a year of experience in the intensive early intervention behavior therapy program, and who has mastered the competencies of a four-month internship. This person provides up to 650 hours of direct case-management and staff and parent training to the family per year. In addition, the one-to-one therapists also provide co-therapy hours with each other to conduct essential therapy tasks in the most cost-effective manner. It may not be cost-effective to require senior-level staff to provide these co-therapy hours. The therapists provide up to a total of 1800 hours of such one-to-one therapy per year. As a result of the cost-effective interaction of this comprehensive team, the "direct co-therapy hours" can be kept within 25% of the total hours, thus conforming to standard practices for direct and indirect time.

How many hours should be authorized?

The intensity of treatment of each individual child should be individualized to their own needs, and for varying durations. Some children benefit from a few hours a week for less than six months, and others require many hours a week for several years. When children use a few hours during the week, those hours should be delivered by senior clinicians, and when children are treated more intensively, a higher proportion of junior clinicians can be used, while under frequent direct clinical supervision.

Each child's optimum intensity should be authorized based upon their responsiveness to treatment. This is measured by an ABA system of directly measured short-term objectives every six months. The common ratio of the hours of different direct services is as follows:

Table 1: Average Hours of Intensity of Evidence Based Treatment

	Comprehensive EIBI Treatment		Focused ABA Treatment	Parent and Caregiver ABA Training
	Intensive Phase	Transition Phase		
	Average Hours of Direct Behavior Analyst Services per Six Months			
Periodic Case Review	38	38	26	26
	Average Hours of Direct Behavior Analyst Services per Week			
Behavior Assessment, Analysis, and ITP Development	4	4	1	1
Clinical Direction	3	1	1	0
Parent and Caregiver Training	6	6	6	6
Clinical Consultation and Case Management	2	2	1	2
	Average Hours of Direct Behavior Technician Services per Week			
Behavior Intervention	40	10	10	0

The common ranges of hours delivered, after individualization, are as follows:

Table 2: Common Ranges of Intensity of Evidence Based Treatment Across the Varying Treatment Models

Treatment Model	Behavior Analyst			Behavior Technician		
	Range of Hours per Week		Average	Range of Hours per Week		Average
	Low	High	per Week	Low	High	per Week
All Models	1.5	25	7	2	60	20
Comprehensive Intensive	1.5	25	18	6	60	30
Comprehensive Transition	2	24	8	-	-	-
Focused	2	10	6	2	16	10
Parent Training	1.5	8	2	-	-	-

What are the optimal payment rates for cost-effective hourly authorization?

The following proposed rates are aligned along a similar range as current rates. However they can result in a more cost effective utilization if the restrictions of the current system are eliminated. If payment were to be made using these rates, without the service pattern restrictions, the provider will no longer profit only when delivering the full level of services, while failing to afford the delivery of reduced services or uncompensated supervision patterns. Without service restrictions, the providers will have no disincentive to transition children out of the program, and instead will have an incentive to deliver the optimum (lesser) level of intensity, and to deliver rural services.

Table 3: Proposed cost effective reimbursement rates without arbitrary service restrictions

Weekly Clinical Role					Provider Type	Service	Cost Per Hour	Cost per Role
Supervision	Assessment	Direction	Intervention	Support				
Supervision	Assessment	Direction	Intervention		Professional (CNS-MH; LICSW; LMFT; LPCC; LP; NP; Psychiatrist; BCBA-D)	Behavior Analyst Case Review and Clinical Management	93.00	84.00
Supervision	Assessment	Direction	Intervention		BCBA Behavior Analyst	Behavior Analyst Assessment, Consultation, and Clinical Direction	75.00	
	Assessment	Direction	Intervention		BCaBA Behavior Therapist	Behavior Analyst Assessment, Training and Case Management	56.00	56.00
	Assessment		Intervention		RBT Bachelor's level Behavior Technician	Behavior Therapy and Training	48.00	40.00
	Assessment		Intervention		RBT Associate Degree Behavior Technician	Behavior Therapy	32.00	
				Support	PCA High School Diploma Respite Provider	Respite and Community Supervision	16.24	16.24

What are the disincentives in current payment systems?

The restrictions upon the types of staff that can deliver services, and upon the patterns of staffing should be based on the evidence in ABA and EIBI. Shrewd payment systems can eliminate disincentives to reduce intensity and to transition children out of treatment. They can also reduce disincentives to deliver less intensive focused services. Disincentives occur when the provider is not reimbursed to fully evaluate the child's needs and monitor treatment quality and effectiveness. Disincentives also occur when the provider is not reimbursed for the excess costs of the senior professionals to make a transition to less intense services. They occur when the provider is not reimbursed to deliver rural services because the rate of reimbursement for transportation doesn't match the costs. They also occur when the provider is only reimbursed for one-to-one child services, when less intense parent or caregiver training would be equally effective.

Table 4: Common restrictions on service patterns that create disincentives for optimizing the intensity of treatment.

1. Only certain professionals can bill for clinical supervision, when the evidence in early intervention research shows that the BCBA-level professional can operate effectively as part of a team and supervise parents and other practitioners cost effectively. This reduces accessibility of services because there are very few qualified mental health professionals available to conduct the extensive weekly supervision duties required.
2. The child must be present for every activity, even when discrete parent training or school consultation is advisable. This interferes with effective treatment planning.
3. Two practitioners cannot bill for simultaneous services, even while other professionals can. This arbitrary distinction ignores the evidence base on the qualifications of behavior analyst supervisors, interferes with continuity of care on a regular basis, slows down progress when two therapists are necessary for assessment or intervention, interferes with effective parent training, and interferes with the safety of dangerous children.
4. Case management is not covered. This prevents the team from coordinating the services of multiple persons and multi-disciplinary services.

Review of published research on high intensity supervision and training.

The use of extensive and intensive clinical supervision is pervasive in the rich evidence base of Applied Behavior Analysis. As soon as ABA programs emerged from the laboratory and moved into implementation in large systems, behavior analysts turned their attention to the need for cost-effective supervision and integrated training systems (Christian & Hannah, 1983; Reid, Parsons, & Green, 1989; Paul & Lentz, 1977). As of today, a vast literature of ABA supervision, management, and training exists. Common evidence-based features include regular direct clinical observation, direct-training-based performance management for continuity of care, and system-wide evaluation to ensure cost-effective implementation (Christian, Hannah, & Glahn (1984). Each of these efforts require substantial cost, time and expertise, and therefore the cost-effectiveness of various staffing levels is always found to be paramount (Lovaas & Buch, 1992; Luce, Christian, Anderson, Troy, & Larsson, 1992; Smith, Parker, Taubman, & Lovaas, 1992). Evidence for the medical necessity of these cost-effective levels of direct clinical supervision is continues to be found in research from these foundational studies to today (Green, Rollyson, Passante, & Reid, 2002; LeBlanc, Gravina, & Carr, 2009).

What follows is a review of ABA research on clinical supervision and management services that have been found to be essential to the implementation of medically necessary treatment in early intervention.

Davis, Smith, & Donohoe (2002) described the UCLA supervision model as consisting of a highly experienced Case Supervisor who oversees three to five children. Each of those children in turn has their own BCaBA Therapist who oversees the child's treatment team daily. In addition to extensive experience, the Case Supervisor also has Board Certified Behavior Analyst skills and is supervised weekly by the Project Director. They concluded that it is of considerable importance to have procedures for evaluating supervisors. In this study they found evidence for a variety of components of a comprehensive strategy for doing so. In each of these cases, the direct clinical supervision was provided by Behavior Analyst Clinical Supervisors and BCaBA Behavior Therapists with master's and bachelor's level pre-service training, who delivered their services within an integrated service delivery system.

Lovaas (1987) is one of the earlier large-scale studies of intensity of treatment. Families in that study received "more than 40 hours of one-to-one treatment per week" by "well-trained student therapists." In addition, "the parents worked as part of the treatment team throughout the intervention; they were extensively trained in the treatment procedures so that treatment could take place for almost all of the subjects' waking hours, 365 days a year." In the report itself, the description of supervision and training was put simply: "It is unlikely that a therapist or investigator could replicate our treatment program for the experimental group without prior extensive theoretical and supervised practical experience in one-to-one behavioral treatment." See Table 5 for a summary of the levels of supervision that were specified as

treatment variables in the studies that are most often cited as the best evidence for Early Intensive Behavioral Intervention.

What level of intensity is commonly found effective?

In the studies that are most often cited as the best evidence for comprehensive interventions, and also are the largest studies, in terms of number of participants and length of time studied (Chorpita et al. 2011; Myers & Johnson, 2007; New York State Department of Health, 1999; Rogers & Vismara, 2008; Warren, et al. 2011), the following independent variables (experimental conditions) were compared with less intensive treatments.

Table 5: Evidence-Based Levels of Behavior Analysis and Behavior Therapy in Outcome Studies

Study	Reported Hours of One-to-One Behavior Therapy	Additional Levels of Behavior Analysis, Assessment, and Direction	Parent Training	Clinical Reviews
Lovaas 1987	An average of 40 hours, with frequent co-therapy, range: 10 to 60 hours per week	Daily to weekly direct supervision by direct supervisor, clinical supervisor, and psychologist	The parents also received extensive instruction and supervision on appropriate treatment techniques for 5-8 hours per week	Weekly team clinical review meeting
Cohen et al. 2006	35 to 40 hours	Clinic Supervisors provided ongoing performance feedback	Weekly parent training	Weekly team clinical review meeting & six-month clinical review
Sallows & Graupner 2005	An average of 37 to 39 hours	6 to 10 hours of weekly co-therapy by the senior therapist and weekly supervision by the clinic supervisor	Parents attended weekly team meetings and extended treatment throughout the day	2 weekly 1-hr team clinical and progress review meetings
Howard et al. 2005	35 to 40 hours	Direct observational data reviewed by program supervisors several times per week	Weekly to monthly parent training	
Eikeseth et al. 2002, 2007	28 hours of school-based and additional home-based parent therapy	10 hours per week of apprentice observation and supervision by supervisors, weekly supervision by project directors	4 hours per week of parent training	2 hour meeting weekly
Hayward, et al. 2009	42 hours of scheduled, home- and school-based treatment	5 hours per week of programme consultant supervision. 11 hours per week of senior tutor supervision. 2 hours per month by programme director	2 to 5 hours per week of parent training	2 hour meeting weekly

While data on the extensive level of supervision in Lovaas (1987) was not kept; in a follow-up paper, Lovaas's colleagues (Leaf, Taubman, & McEachin, 2008) described the level of supervision and training,

which went beyond the 40 hours, in detail. “The nineteen children in the intensive treatment group received an average of 40 man-hours of formal ABA intervention weekly. Man-hours were counted because there were sessions with two therapists, done for training purposes and to maximize the instructional time as well as permit teaching observational learning and other skills requiring a second person.” “Each treatment team was supervised by a graduate student in psychology or an advanced undergraduate student. Dr. Lovaas and the clinic supervisor provided clinical oversight.” “After demonstrating a thorough understanding of the principles of ABA, staff attended a series of workshops.” “Staff received further training when they worked with the children. Typically, new staff worked alongside a more experienced staff member for several weeks. Additionally, the supervisor often accompanied staff to provide additional training.” “When a child was progressing slowly, therapy hours were increased to help facilitate progress.” “Supervision occurred on a frequent and ongoing basis (i.e., a minimum of weekly and often daily). Multiple layers of supervision were provided. In addition to the direct supervisor, a clinical supervisor and psychologist provided oversight to each case.” “It was standard practice to have two therapists work every session.” “Over time we have seen that double therapy can have tremendous clinical benefit. Then as now, we find using two therapists can make the sessions more productive in a number of ways:
- Simulation of play dates
- Simulation of school
- Increased opportunities to practice observational learning and group instructions
- Reduced "downtime" during set-up and record keeping, and
- Increase in staff’s skills”

Cohen et al. (2006) qualitatively described the following levels of supervision beyond the research description of 35 to 40 hours per week of one-to-one. “To ensure proficiency in implementing the UCLA model, 5 CVAP staff members each completed 3- to 4-month internships at UCLA, and consultants from UCLA made on-site visits 2 to 4 times per year for the first 3 years of the study period, with frequent telephone contacts between visits (typically once per week).” “Clinic supervisors trained and provided ongoing performance feedback to tutors. Supervisors were graduate students in behavior analysis or master’s level clinicians with 2 or more years of experience in providing EIBT.” “At the beginning of treatment, all parents attended a 12- to 18-hour training workshop across 2 to 3 days on behavioral principles and intervention methods. Thereafter, they participated in weekly training sessions to generalize their child’s newly established skills to the natural environment.”

Sallows and Graupner (2005) provided more quantitative data. They reported the following levels of supervision for an intensive treatment group that averaged 37 to 39 hours per week of one-to-one. A Senior Therapist delivered 6 to 10 hours per week in 3 co-therapy sessions per family. A Clinical Supervisor or Director conducted a weekly 1-hour Clinical Review Meeting. A Team Meeting was held for 1 hour per week. Each staff received 20 hours of PreTraining. Each Senior Therapist received 4 months of continuous co-therapy prior to taking on that role independently. The Clinic Director provided weekly supervision.

Howard et al. (2005) reported 35 to 40 hours per week of one-to-one intervention for children aged 3 and older, with supervision as follows: “Direct observational data on each child’s progress were reviewed by program supervisors several times each week, and intervention procedures were modified as needed.” One-to-one staff “were trained and supervised by staff with master’s degrees in psychology or special education and coursework as well as supervised practical experience in applied behavior analysis with children with autism. Some supervisors were assisted by staff with bachelor’s degrees and (typically) graduate coursework in behavior analysis. Each supervisor was responsible for programming for 5–9 children and worked under the direction of a Board Certified Behavior Analyst who was also a licensed psychologist and a licensed speech and language pathologist. Parents received training in basic behavior analytic strategies, assisted in the collection of maintenance and generalization data, implemented programs with their children outside of regularly scheduled intervention hours, and met with agency staff one to two times a month.” “efforts were made to ensure treatment integrity (e.g., through frequent direct observation and videotaping of staff implementing procedures with children, and frequent feedback from supervisors).”

Eikeseth et al. (2002, 2007) reported on children who received 28 hours per week of school-aged one-to-one services by teachers and therapists, and additional parent treatment at home. “During the study, the therapists received 10 hours per week of supervision in an apprenticeship format: Supervisors set up and implemented treatment programs, and then the therapists implemented these programs and received feedback based on supervisors' in vivo observations of their work.” “They [Supervisors] met weekly with the project directors, each of whom were psychologists with approximately 10 years of experience implementing the UCLA treatment prior to the study.” “Weekly, 2-hour meetings were held for each child. The child, primary caregiver, therapists, supervisor, and director attended.” “Parental participation was considered central to the treatment. As part of their training, parents worked alongside therapists at school for the first 3 months of treatment for a minimum of 4 hours per week.”

Hayward et al. (2009) reported on children who received 42 scheduled hours per week of home-based treatment. “Each child is assigned a programme consultant, providing 5 h per week of supervision, for 46 weeks per year. Supervision is distributed as follows: weekly 2 h team meeting; in home supervision during treatment sessions; school consultations; supervision to the senior tutor; meetings with parents; meetings with school staff and other professionals involved with the child; clinical administrative tasks related to the case, such as programming, task analysis and functional assessment.” “A senior tutor is provided for each child for a minimum of 11 h per week, for 46 weeks of the year. The main duties of the senior tutor are to assist in running team meetings, provide one-to-one teaching and supervise tutors during one-to-one teaching, as well as to conduct related clinical administrative tasks.” “A director also provides supervision to each child, for a minimum of 2 h per month.” “A weekly 2 h team meeting is conducted during which all team members, including parents, participate. During these meetings all team members work with the child on his/her current programmes. This enables the team, and in particular the programme consultant and senior tutor, to provide feedback on teaching procedures and progress. It also enables them to review the curriculum and interventions and revise them for the following week. Detailed notes are typed during the team meeting, based on the conclusions of all advice that was given and discussions that have been held. The team then follows this advice throughout the next week of teaching.” “Close supervision is also provided by programme consultants and directors on ongoing clinical practice and on development of professional and managerial skills, such as working closely with parents and other professionals, making presentations and supervising and appraising tutors.”

Eikeseth et al. (2009) reported a significant correlation between the IQ gains and the intensity of supervision of children served by intensive parent-managed services. In these outreach services, children received an average of 34 hours per week of one-to-one treatment, and the level of supervision ranged from 2.9 to 7.8 hours per month. The level of supervision correlated at .45 with the change in IQ over the first 14 months of treatment, producing an average gain of .21 IQ points per hour of supervision. The average IQ gain was 17 points. Eikeseth concluded, “intensity of supervision together with intensity of treatment, treatment method, and pretreatment functioning are variables that may affect outcome for children with autism who receive early and intensive behavioral intervention.”

Research on treatment with low levels of supervision. For comparison purposes, Leaf, Taubman, & McEachin (2008) summarized the components of high intensity supervision as follows: Staff hired and trained by agency; One to two months of pre-training; Weekly and sometimes daily supervision; Weekly Clinical Review Meetings; High level of expertise in Clinical Supervision. In contrast, they summarized low intensity supervision as being comprised of: Staff hired by parents; Staff trained through consultation; Three days of pre-training; Monthly to quarterly consultation; Monthly to quarterly Clinical Review Meetings; Poorly controlled supervisor expertise. In comparison to the high intensity studies reviewed above, several studies of low intensity supervision have also been conducted. In each of these studies, the levels of recovery from autistic symptoms have been much less (Smith, Buch, & Gamby, 2000; Smith, Groen, & Wynn, 2000; Remington, et al., 2007). In some reports of early intervention where limited gains were found (Bibby, et al., 2002; Magiati, et al., 2007), the reported levels of supervision have been as low as only once every 3 months.

Smith and Wynn (2003) described the preliminary results of the long-term replication study of the Lovaas (1987) results. In describing the control group treatment of low intensity supervision workshops, “it appears that the percentage of children who achieve normal functioning (average levels of intelligence and satisfactory, unassisted performance in a class for typically developing children) is estimated at closer to

10% or 20% rather than the 47% reported for clinic-based treatment at UCLA (Lovaas, 1987). This lower rate may reflect such factors as high staff turnover, less frequent supervision than that which occurs in clinic-based treatment, and the use of aides with less academic background in learning-based theory and research than those provided by UCLA, LIFE, and replication sites."

Lovaas and Smith (2003) described the standard Lovaas multi-site replication protocol for supervision and training as a result of the above research: "In clinic-based services each member of the child's team, Student Therapists, Senior Therapist, Case Supervisor and Clinic Supervisor, has passed quality control. Each child is reviewed in weekly Clinic Meetings of one to two hour duration." "A Senior Therapist may not be able to effectively supervise the treatment of more than 2 children, each receiving a total of 40 hours of one-on-one treatment per week. A Case Supervisor supervises about 4 children providing no less than 4 hours supervision per child per week in cooperation with a child's Senior Therapist and helps train Student Therapists. It is our experience that a Clinic Director can provide effective supervision of no more than 14 children at any one time given that 14 children would be receiving 560 hours of treatment per week. Both Case and Clinic Supervisors are available to the child's parents to help answer questions about treatment, assist in staff training and participate in research. The intensity and close supervision of the treatment provide opportunities for identifying ineffective and harmful treatments and development and testing of effective ones."

Bibliography

American Academy Of Pediatrics (2001). Policy Statement: The Pediatrician's Role in the Diagnosis and Management of Autistic Spectrum Disorder in Children (RE060018) *Pediatrics,* 107, 1221-1226. http://www.aap.org/policy/re060018.html

American Psychological Association Division 53: Society of Clinical Child and Adolescent Psychology. Review of Evidence-Based Mental Health Treatment for Children and Adolescents, including Autism. http://effectivechildtherapy.com/sccap/?m=sPro&fa=pro_ESToptions#sec13 Accessed November 29, 2010

Autism Society of America (1998) Intensive Behavioral Intervention. Informational handout downloaded from www.autism-society.org

Autism Speaks (2012) Applied Behavior Analysis (ABA). Downloaded from http://www.autismspeaks.org/what-autism/treatment/applied-behavior-analysis-aba on November 2, 2012.

Baker, B.L. & Feinfield, K.A. (2003). Early intervention. *Current opinion in psychiatry.* 16, 503-509.

Barbaresi, W.J., Katusic, S.K., & Voigt, R.G. (2006). Autism: A review of the state of the science for pediatric primary health care clinicians. *Archives of Pediatric and Adolescent Medicine*, 160. 1167-1175.

Bibby, P., Eikeseth, S., Martin, N. T., Mudford, O. C., & Reeves, D., (2002). Progress and outcomes for children with autism receiving parent-managed intensive interventions. *Research in Developmental Disabilities*. 23, 81-104.

Bregman, J.D. & Gerdtz, J. (1997). Behavioral Interventions. In D.J. Cohen & F.R. Volkmar, (Eds.), *Handbook of Autism and Pervasive Developmental Disorders* (pp. 606-630). New York: Wiley.

Bregman, J.D., Zager, D. & Gerdtz, J. (2005). Behavioral interventions. In F.R. Volkmar, R. Paul, A. Klin, & D. Cohen (eds.) *Handbook of Autism and Pervasive Developmental Disorders.* New York: John Wiley & Sons. 897-924.

California Legislative Blue Ribbon Commission on Autism (2007). *Report: An Opportunity to Achieve Real Change for Californians with Autism Spectrum Disorders*. Sacramento, CA: The Legislative Office Building. Available online at: http://senweb03.sen.ca.gov/autism

Centers for Disease Control (2012) Autism Spectrum Disorders. Downloaded from http://www.cdc.gov/ncbddd/autism/treatment.html on November 2, 2012.

Chorpita, B.F. & Daleiden, E.L. (2007). *2007 Biennial report: Effective psychosocial interventions for youth with behavioral and emotional needs.* Child and Adolescent Mental Health Division, Honolulu: Hawaii Department of Health.

Chorpita, B.F. & Daleiden, E.L. (2009). *2009 Biennial Report: Effective psychosocial interventions for youth with behavioral and emotional needs.* Child and Adolescent Mental Health Division, Honolulu: Hawaii Department of Health. Available online at: http://hawaii.gov/health/mental-health/camhd/library/pdf/ebs/ebs013.pdf

Chorpita, B.F. et al. (2011). Evidence-based treatments for children and adolescents: An updated review of indicators of efficacy and effectiveness. *Clinical Psychology Science and Practice*. 18, 154-172.

Christian, W.P., & Hannah, G.T. (1983). *Effective management in human services.* Englewood Cliffs, NJ: Prentice Hall.

Cohen, H., Amerine-Dickens, M., & Smith, T., (2006). Early Intensive Behavioral Treatment: Replication of the UCLA model in a community setting. *Developmental and Behavioral Pediatrics*, 27, S145-S155.

Committee on Children With Disabilities (2001). Technical Report: The Pediatrician's Role in the Diagnosis and Management of Autistic Spectrum Disorder in Children. *Pediatrics,* 107, e85. http://www.pediatrics.org/cgi/content/full/107/5/e85

Davis, B.J., Smith, T., & Donahoe, P. (2002). Evaluating supervisors in the UCLA treatment model for children with autism: Validation of an assessment procedure. *Behavior Therapy*, 33, 601–614.

Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology*. 20, 775-803. doi:10.1017/S0954579408000370.

Dawson, G. & Burner, K. (2011). Behavioral interventions in children and adolescents with autism spectrum disorder: A review of recent findings. *Current Opinion in Pediatrics*, 23, 616-620 doi:10.1097/MOP.0b013e32834cf082

Eikeseth, S., Smith, T., Jahr, E., & Eldevik, S. (2007) Outcome for children with autism who began intensive behavioral treatment between ages 4 and 7: A comparison controlled study. *Behavior Modification*, 31, 264-278.

Filipek, P.A. et al. (1999). The screening and diagnosis of autistic spectrum disorders. Journal of Autism and Developmental Disorders. 29, 439-484.

Frazier, T.W., Youngstrom, E.A., Haycook, T., et al. (2010). Effectiveness of medication combined with intensive behavioral intervention for reducing aggression in youth with autism spectrum disorder. *Journal of Child and Adolescent Psychopharmacology*, 20, 167–177.

Hayward, D.W., Gale, C.M., & Eikeseth, S. (2009). Intensive behavioural intervention for young children with autism: A research-based service model. *Research in Autism Spectrum Disorders*, 3, 571-580.

Helt, M., Kelley, E., Kinsbourne, M., Pandey, J., Boorstein, H., Herbert, M., & Fein, D. (2008). Can children with autism recover? If so, how? *Neuropsychology Review*. 18, 339-366.

Howard, J.S., Sparkman, C.R., Cohen, H.G., Green G., & Stanislaw H. (2005). A comparison of intensive behavior analytic and eclectic treatments for young children with autism. *Research in Developmental Disabilities*. 26, 359-383.

Howlin, P., Magiati, I., & Charman, T., (2009). Systematic review of early intensive behavioral interventions for children with autism. *American Journal on Intellectual and Developmental Disabilities*. 114:23–41. doi:10.1352/2009.114:23;nd41. PMID 19143460.

Johnson, E., & Hastings, R.P. (2002). Facilitating factors and barriers to the implementation of intensive home-based behavioural intervention for young children with autism. *Child Care Health and Development*. 28, 123-129.

Koegel, R.L., Koegel, L.K., Vernon, T.W., & Brookman-Frazee, L.I. (2010). Empirically supported pivotal response treatment for children with autism spectrum disorders. In J.R. Weisz & A.E. Kazdin (Eds.), *Evidence-Based Psychotherapies for Children and Adolescents*. New York: Guilford. 327-344.

Leaf, R., Taubman, M., & McEachin, J. (2008). *Sense and nonsense in the behavioral treatment of autism: It has to be said.* New York, NY: DRL Books, Inc.

LeBlanc, L.A., Gravina, N., & Carr, J.E. (2009). Training issues unique to autism spectrum disorders. In Matson, J.L. (Ed.), *Applied behavior analysis for children with autism spectrum disorders*, New York, NY: Springer Science+Business Media, DOI 10.1007/978-1-4419-0088-3_13.

Levy, S.E., Mandell, D.S., & Schultz, R.T. (2009). Autism. *Lancet*. 374, 1627-1638.

Lovaas, O.I. (1987). Behavioral treatment and normal educational and intellectual functioning in young autistic children. *Journal of Consulting and Clinical Psychology*. *55*, 3-9.

Lovaas, O.I., & Buch, G. (1992). Editor's Introduction. *Research in Developmental Disabilities.* 13, 1-7.

Lovaas, O.I., & Smith, T. (2003). Early and intensive behavioral intervention in autism. In A.E. Kazdin & J.R. Weisz (Ed.), *Evidence-Based Psychotherapies for Children and Adolescents* (pp. 325-340). New York: Guilford.

Luce, S.C., Christian, W.P., Anderson, S.R., Troy, P.J., & Larsson, E.V. (1992). Development of a continuum of services for children and adults with autism and other severe behavior disorders. *Research in Developmental Disabilities*, 13, 9-25.

Maine Administrators of Services for Children with Disabilities (2000). *Report of the MADSEC Autism Task Force, Revised Edition..* Kennebec Centre, RR 2 Box 1856, Manchester, ME 04351, http://www.madsec.org/docs/atf.htm

Maurice, C. (2001). Autism advocacy or trench warfare? In C. Maurice, G. Green, & R.M. Foxx (Eds.), *Making a difference: Behavioral intervention for autism* (pp. 1-9). Austin, TX: Pro-Ed.

Mudford, O.C., Martin, N.T., Eikeseth, S., & Bibby, P. (2001). Parent-managed behavioral treatment for preschool children with autism: Some characteristics of UK programs. *Research in Developmental Disabilities*, 22, 173-182.

Myers, S.M., Johnson, C.P. & the American Academy of Pediatrics Council on Children With Disabilities, (2007). Management of children with autism spectrum disorders. *Pediatrics*. 120, 1162–1182. doi:10.1542/peds.2007-2362. PMID 17967921. Available online at http://aappolicy.aappublications.org/cgi/reprint/pediatrics;120/5/1162.pdf. Accessed November 27, 2007.

National Institute of Mental Health (2008). Autism Spectrum Disorders: Pervasive Developmental Disorders. NIH Publication no. 08-5511.

National Research Council (2001). *Educating Children with Autism,* Committee on Educational Interventions for Children with Autism, Division of Behavioral and Social Sciences and Education, Washington, D.C.: National Academy Press. http://books.nap.edu/books/0309072697/html/index.html

New York State Department of Health Early Intervention Program (1999). *Clinical Practice Guideline: Report of the Recommendations, Autism/Pervasive Developmental Disorders, Assessment and Intervention for Young Children.* Publication #4215. Health Education Services, P.O. Box 7126, Albany, NY 12224. http://www.health.state.ny.us/nysdoh/eip/menu.htm

Paul, G.L. & Lentz, R.J. (1977). *Psychosocial treatment of chronic mental patients: Milieu versus social-learning programs.* Cambridge, MA: Harvard University Press.

Perry, A., Cummings, A., Geier, J. D., Freeman, N. L., Hughes, S., LaRose, L., Managhan, T., Reitzel, J.A., & Williams, J. (2008). Effectiveness of intensive behavioral intervention in a large, community-based program. *Research in Autism Spectrum Disorders*, 2, 621–642.

Reichow, B. & Volkmar, F. (2010). Social skills interventions for individuals with autism: evaluation for evidence-based practices within a best evidence synthesis framework. *Journal of Autism and Developmental Disorders*, 40, 149–166.

Reichow, B., Volkmar, F.R., & Cicchetti, D.V. (2008). Development of the evaluative method for evaluating and determining evidence-based practices in autism. *Journal of Autism and Developmental Disorders.* 38, 1311-1319.

Reid, D. H., Parsons, M. B., &, Green, C. W. (1989). *Staff management in human services: Behavioral research and application.* Springfield, IL: Charles C. Thomas.

Remington, B., Hastings, R.P., Kovshoff, H., degli Espinosa, F., Jahr, E., Brown, T., Alsford, P., Lemaic, M., & Ward, N. (2007). Early intensive behavioral intervention: Outcomes for children with autism and their parents after two years. *American Journal on Mental Retardation.* 112, 418-438.

Rimland, B. (1994). Recovery from autism is possible. *Autism Research Review International*, 8, 3.

Rogers, S.J. (1998). Empirically supported comprehensive treatments for young children with autism. *Journal of clinical child psychology.* 27. 167-178.

Rogers, S.J., & Vismara, L.A. (2008). Evidence-based comprehensive treatments for early autism. *Journal of Clinical Child and Adolescent Psychology*. 37:8–38. doi:10.1080/15374410701817808. PMID 18444052.

Sallows, G.O., & Graupner, T.D. (2005). Intensive behavioral treatment for children with autism: Four-year outcome and predictors. *American Journal on Mental Retardation*, 110, 417-438.

Satcher, D. (1999). *Mental health: A report of the surgeon general.* U.S. Public Health Service. Bethesda, MD. Available at: http://www.surgeongeneral.gov/library/mentalhealth/chapter3/sec6.html#autism

Simeonsson, R.J., Olley, J.G., & Rosenthal, S.L. (1987). Early intervention for children with autism. In M.J. Guralnick & F.C. Bennett (Eds.) *The effectiveness of early intervention for at-risk and handicapped children.* (pp. 275-296). Orlando FL: Academic Press.

Smith, T. (2010). Early and intensive behavioral intervention in autism. In J.R. Weisz & A.E. Kazdin (Eds.), *Evidence-Based Psychotherapies for Children and Adolescents*. New York: Guilford. 312-326.

Smith, T., & Wynn, J.W. (2003). Considerations in the selecting consultants for home-based programs. In O.I. Lovaas, (Ed.) *Teaching individuals with developmental delays: Basic intervention techniques.* Austin, TX: Pro-Ed.

Smith, T., Buch, G.A., & Gamby, T.E. (2000). Parent-directed, intensive early intervention for children with pervasive developmental disorder. *Research in Developmental Disabilities, 21*, 297-309.

Smith, T., Groen, A.D., & Wynn, J.W. (2000). Randomized trial of intensive early intervention for children with pervasive developmental disorder. *American Journal on Mental Retardation. 105*, 269-285.

Smith, T., Parker, T., Taubman, M., & Lovaas, O.I. (1992). Transfer of staff training from workshops to group homes: a failure to generalize across settings, *Research in Developmental Disabilities.* 13, 57-71.

Vismara, L.A. & Rogers, S.J. (2010). Behavioral treatments in autism spectrum disorder: What do we know? *Annual Review of Clinical Psychology* 6, 447-468.

Volkmar, F., Cook, E.H., Pomeroy, J., Realmuto, G. & Tanguay, P. (1999). Practice parameters for the assessment and treatment of children, adolescents, and adults with autism and other pervasive developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry,* 38 (Supplement), 32s-54s.

Warren, Z., McPheeters, M.L., Sathe, N., Foss-Feig, J.H., Glasser, A., & Veenstra-VanderWeele, J. (2011). A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics,* 127, e1303-e1311. doi: 10.1542/peds.2011-0426

Warren, Z., Veenstra-VanderWeele, J., Stone, W., Bruzek, J.L., Nahmias, A.S., Foss-Feig, J.H., Jerome, R.N., Krishnaswami, S., Sathe, N.A., Glasser, A.M., Surawicz, T., McPheeters, M.L. (2011). Therapies for children with autism spectrum disorders. *Comparative Effectiveness Review*, No. 26, Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Young, J., Corea, C., Kimani, J., & Mandell, D. (2010). *Autism spectrum disorders (ASDs) services: Final report on environmental scan.* Columbia, MD: IMPAQ International.

AMA CPT ABA Codes July 2014 Summary

CPT Category III code set:

Tab 101
Applied Behavior Analysis

Adaptive Behavior Assessment

Behavior identification assessment
0359T
Physician or other Qualified Health Care Professional "Professional"
History, observation, tests, interview to describe deficient adaptive or maladaptive behaviors.
Interpretation of results and development of plan of care.
Discussion of findings and recommendations with caregivers.
Preparation of report.

Observational behavioral follow-up assessment
Follows 0359T
0360T 16-45 min
0361T each additional 30 min (List separately in addition to code for primary service)
Professional or Technician under direction of Professional who may or may not be on-site.
Structured observation and/or standardized and non-standardized tests.
Interpretation of results and development of plan of care.
Discussion of findings and recommendations with caregivers.
Preparation of report.
Based on the time that the patient is face-to-face with one or more technician(s). Only count the time of one technician when two or more are present. Report days separately.

Exposure behavioral follow-up assessment
Follows 0359T
0362T 16-45 min
0363T each additional 30 min
Professional with the assistance of the Technician
Exposing the patient to a series of social and environmental conditions associated with Destructive Behavior(s) in a structured, safe environment.
Interpretation of results and development of plan of care.
Discussion of findings and recommendations with caregivers.
Preparation of report.
Based on the time that the patient is face-to-face with one or more technician(s). Only count the time of one technician when two or more are present. Report days separately.

Adaptive Behavior Treatment

Adaptive behavior treatment by protocol
0364T first 30 min
0365T each additional 30 min
Technician under direction of Professional who may or may not be on-site.
Face-to-face with one patient.
Utilizing a behavior intervention protocol designed in advance for deficient adaptive or maladaptive behaviors.
Based on results of previous assessments.

Group adaptive behavior treatment by protocol
0366T first 30 min
0367T each additional 30 min
Technician under direction of Professional who may or may not be on-site.

face-to-face with two to eight patients
Utilizing a behavior intervention protocol designed in advance for deficient adaptive or maladaptive behaviors
Based on results of previous assessments.

Adaptive behavior treatment with protocol modification
0368T first 30 min
0369T each additional 30 min
Professional with or without Technician present.
Face-to-face with one patient.
professional resolves one or more problems with the protocol
may simultaneously instruct a technician and/or guardian(s)/caregiver(s) in administering the modified protocol.
Based on results of previous assessments.

Family adaptive behavior treatment guidance
0370T
Professional with or without Technician present
Face-to-face with guardian(s)/caregiver(s), of one patient, without the presence of a patient,
Involves identifying problem behaviors and deficits and teaching guardian(s)/caregiver(s) to utilize treatment protocols designed to reduce maladaptive behaviors and/or skill deficits.
Based on results of previous assessments.

Multiple-family group adaptive behavior treatment guidance
0371T
Professional
Face-to-face with guardian(s)/caregiver(s), of two to eight patients, without the presence of a patient,
Involves identifying problem behaviors and deficits and teaching guardian(s)/caregiver(s) to utilize treatment protocols designed to reduce maladaptive behaviors and/or skill deficits.
Based on results of previous assessments.

Adaptive behavior treatment social skills group
0372T
Professional
Face-to-face with two to eight patients,
Focusing on social skills training and identifying and targeting individual patient social deficits and problem behaviors.
Based on results of previous assessments.

Exposure adaptive behavior treatment with protocol modification
0373T first 60 minutes of technicians' time,
0374T each additional 30 minutes of technicians' time
Technician under supervision of Professional
Face-to-face with patient
Services provided to patients with one or more specific severe maladaptive behaviors with direct supervision by a Professional which requires two or more technicians face-to-face with the patient for safe treatment.
Technicians elicit behavioral effects of exposing the patient to specific environmental conditions and treatments.
The Professional reviews and analyzes data and refines the therapy using single-case designs
The therapy is conducted in a structured, safe environment.

Treatment for Gender Dysphoria 2014

Question: What therapies should be included for treatment of gender dysphoria on the Prioritized List?

Question Source: HERC staff, OHA

Issue:
The October 1, 2014 Prioritized List includes Gender Dysphoria as a new, covered line (413). Currently, the only treatments on this line are office visits, psychotherapy and puberty suppression medication for transgender and gender-questioning youth. Other treatments for gender dysphoria include cross-sex hormone therapy and sex reassignment (gender reassignment) surgery.

Cross-sex hormone therapy and sex reassignment surgery were reviewed at the May, 2014 VBBS meeting. At that time, literature was reviewed which found that cross-sex hormone therapy, in conjunction with psychotherapy, may offer some benefit in self-reported outcomes for persons with gender dysphoria based on poor quality evidence. Gender reassignment surgery in conjunction with hormone therapy likely improves gender dysphoria, psychological functioning and comorbidities, sexual function and overall quality of life. Most major professional societies and evidence-based health systems such as the NHS recommend cross-sex hormone therapy and sex reassignment surgery be available for appropriate patients who meet strict eligibility criteria. The evidence for both cross-sex hormone therapy and gender reassignment surgery is of poor quality. Outcomes for gender reassignment surgery appear good, with no patients reporting regrets. Outcomes for cross-sex hormone therapy are generally positive, with some medical complications noted in female to male transitioning patients.

The literature review and expert testimony indicated that people with gender dysphoria had a much higher than average rate of suicide, suicide attempts, IV drug abuse, HIV positivity and other high risk behavior/conditions. Experts testified that treatment of gender dysphoria with a range of options including cross-sex hormone therapy and sex reassignment surgery reduced the morbidity of this condition. Experts also testified that treatment of this condition had been shown in California to have negligible economic impact on the health plans.

HERC staff was charged with finding further information on the morbidity/mortality of gender dysphoria and what, if any, impact treatment of this condition had on morbidity, particularly suicide attempts. HERC staff was also charged with finding information on cost experience in states that have covered treatments of gender dysphoria including cross-sex hormone therapy and sex reassignment surgery.

HERC staff was asked to mock up a line for sex reassignment surgery with appropriate scoring. If the scoring for this line placed it in close proximity to the existing gender dysphoria line, staff should propose a single line with all therapies.

Treatment for Gender Dysphoria 2014

Evidence Summary

Studies on suicide rates among patients with gender dysphoria

1) **Blosnich 2013**
    a. N=3177, VA patients
    b. The rate of suicide-related events among GID-diagnosed VHA veterans was more than 20 times higher than were rates for the general VHA population.

Effect of gender dysphoria treatment on psychiatric outcomes

1) **Heylens 2014**, prospective cohort study of effects of cross-sex hormone therapy and gender reassignment surgery
    a. N=57, Belgium, 4 yr follow up
    b. The overall psychoneurotic distress scores decreased significantly after hormone therapy, ($P < 0.001$). No further decrease is observed after sex reassignment surgery.
    c. Unlike scores at time of presentation, SCL-90 scores after hormonal treatment and after surgery are similar to the mean SCL-90 scores of a general population.
    d. Significant reductions seen in scores for anxiety and depression after treatment
2) **Colizzi 2014**, cohort study of psychological effects of initiation of cross-sex hormone therapy
    a. N=118 patients, follow up 12 months, Italy
    b. Psychiatric distress and functional impairment were present in a significantly higher percentage of patients before starting the hormonal treatment than after 12 months (50% vs. 17% for anxiety; 42% vs. 23% for depression; 24% vs. 11% for psychological symptoms; 23% vs. 10% for functional impairment).
2) **Gomez-Gil 2012**, cohort study of effects of cross-sex hormone therapy
    a. N=187 (120 treated, 67 not treated)
    b. SADS, HAD-A, and HAD-Depression (HADD) mean scores were significantly higher among patients who had not begun cross-sex hormonal treatment compared with patients in hormonal treatment ($p = .038$; $p = .001$; $p = .002$ respectively). Similarly, current symptoms of anxiety and depression were present in a significantly higher percentage of untreated patients than in treated patients (61% vs. 33% and 31% vs. 8% respectively).
3) **Dhejne 2011**, cohort study of outcomes of gender reassignment surgery
    a. N=324, Sweden, 30 year period
    b. Compared outcomes of patients with gender reassignment surgery to general population; no comparison with persons with gender dysphoria who were not treated
    c. Incidence of suicide: 2.7/1000 person-yrs for patients with gender dysphoria compared to 0.1/1000 person-yrs for controls
    d. Incidence of suicide attempts: 7.9/1000 person-yrs vs 1.0/1000 person-yrs
    e. Incidence of substance misuse: 5.9 /1000 person-yrs vs 1.8/1000 person-yrs

4) **Murad 2010**, meta-analysis
    a. Systematic review and meta-analysis of impact of hormonal therapy and sex reassignment on health outcomes
    b. Included 28 observational studies, N = 1833 participants with GID (1093 male-to-female, 801 female-to male) who underwent sex reassignment that included hormonal therapies
    c. Suicide attempt rates decreased after sex reassignment but stayed higher than the normal population rate.
    a. The average reduction was from 30 percent pretreatment to 8 percent post treatment.
5) **Kuhn 2008**, case control study out outcomes of sex reassignment surgery
    a. N=55 patients with gender dysphoria/20 controls, follow up 15 yrs, Switzerland
    b. Quality of life as determined by the King's Health Questionnaire was significantly lower in general health, personal, physical and role limitations. Patients' satisfaction was significantly lower compared with controls. Emotions, sleep, and incontinence impact as well as symptom severity is similar to controls. Overall satisfaction was statistically significant lower in TS compared with controls.
6) **De Cuypere 2006**, cohort study of outcomes of gender reassignment surgery
    a. N-109, The Netherlands, 15 year follow up
    b. Suicide attempt rate: Although the suicide attempt-rate dropped significantly from 29.3% to 5.1% (McNemar test, N = 58, P = 0.004), it was definitively higher than in the average population (0.15%)
7) **Smith 2005**, prospective cohort study of outcomes of gender reassignment surgery
    a. N=162, United Kingdom
    b. After treatment the group was no longer gender dysphoric
    c. Depression scores improved significantly after treatment (29.3%-22.5%)

<u>Evidence summary</u>

Most, but not all, studies found a significant reduction in depression and anxiety and in gender dysphoria symptoms after treatment for gender dysphoria (hormonal, surgical or a combination). Two studies examined cross-sex hormone therapy alone and one study examined cross-sex hormone therapy separately from gender reassignment surgery. These studies found significant improvement in psychiatric health came from cross-sex hormone therapy alone.

In terms of suicide/suicide attempt reduction, one study found significantly higher rates in treated patients with gender dysphoria compared to the general population. However, this study did not compare treated patients to untreated patients. Two studies comparing treated and untreated patients found a suicide attempt rate reduction of approximately 30% pre-treatment to 5-8% post-treatment (hormone therapy, surgery, or a combination).

HERC staff mock-up of surgical treatment line

Line XXX
Condition: GENDER DYSPHORIA
Treatment: SURGICAL TREATMENT
ICD-9: 302.85 (Gender identity disorder in adolescents or adults)
ICD10: F64.x (Gender identity disorder)
CPT: 19301-19304, 53430, 54125, 54400-54417, 54520, 54660, 54690, 55175-55180, 55970, 55980, 56625, 56800, 56805, 56810, 57106-57107, 57110-57111, 57291-57292, 57335, 58150, 58180, 58260-58262, 58275-58291, 58541-58544, 58550-58554, 58570-58573, 58661, 58720, outpatient medical visit codes
HCPCS:G0396,G0397,G0463

Scoring proposal (scoring for line 413 in parentheses)
Category: 6 (7)
HL: 3 (3)
Suffering: 4 (4)
Population effects: 0 (0)
Vulnerable population: 0 (0)
Tertiary prevention: 3 (3)
Effectiveness: 2 (2)
Need for service: 0.8 (1)
Net cost: 2 (2)
Score: 640
Approximate line placement: 369

Actuarial Estimates

Estimate of number of OHP members with gender dysphoria

The classic estimate for prevalence of transgender individuals (using gender identity disorder as a measurement) comes from the 1994 Diagnostic and Statistical Manual, Fourth Edition (DSM-IV), which reported 1:30,000 natal males and 1:100,000 natal females. Some sources cite rates which are 3-8 times higher than the DSM estimate. Assume 1 in 65,000 persons in Oregon has gender dysphoria (average of male/female DSM estimate)

Oregon population: 3,940,065 (2013 US Census) à 61 persons with gender dysphoria.
Upper end of estimate (using 8x DSM estimate) à 448 persons
Oregon Medicaid population: 935,026 (OHA April 2014 data) à 14 persons with gender dysphoria. Upper end of estimate (using 8x DSM estimate) à 112 persons

Claims data: 175 OHP recipients had claims for ICD-9 302.6 and 302.85 for calendar year 2012

HERC staff estimate 175 enrollees on Oregon Medicaid will have gender dysphoria.

Estimate of utilization of OHP members of treatments for gender dysphoria

The City and County of San Francisco (San Francisco) prohibited gender-based discrimination in 2001 for all City and County employees and their dependents. In the following five years, there were only 37 claims. A report by Jamison Green and Associates estimated that utilization rates (claimants per employee) ranged from 0.0325 to 0.104 claimants per thousand employees per year. The University of California released utilization rates in 2012: Average utilization rates 0.062 covered lives.

HERC staff estimate a utilization (of all treatments for gender dysphoria) in the Oregon Medicaid program of 175 persons. Not all of these persons may seek care in any given coverage period.

Estimate of costs for adding all treatments for gender dysphoria

For San Francisco, the initial cost per employee was $1.70 per member per month (PMPM) in 2001. Due to low utilization, San Francisco reduced the PMPM to $1.16 in 2004-2005 and the city's self-insured plan reduced its charge to $0.50 PMPM. As of July 1, 2006, the cost data demonstrated that no separate rate was required, so the charge was removed entirely. Claim cost data from the UC health plan with the largest enrollment shows that the claim costs PMPM attributed to the elimination were very low. The maximum of claim costs during the 6.5 years was $0.20 PMPM, or 0.05 percent of the total premium. For the City of Berkeley, insurers charged a premium of 0.2 percent of the total annual budget for healthcare benefits. The total projected monthly increase was 0.25 percent (223 covered lives in one plan) and 0.19 percent (938 covered lives in another plan) as of March 2012. The cost projection for Portland was $32,302 out of a total $41,615,000 health care budget – a 0.08 percent increase. The City of Seattle absorbed a premium increase of $200,000 per year of a total $105 million health care budget – 0.19 percent of total health costs based on insurer estimates of increased utilization.

HERC staff estimate of PMPM cost: $0.20-$0.50

A preliminary estimate by the New York State Department of Health in 2010 approximated that it would cost about $1.7 million to cover gender-confirming care through Medicaid. As the state Medicaid budget totals $52 billion, this represents only 0.003 percent of the total budget. The Kaiser Family Foundation estimates that Oregon Medicaid total costs for 2012 were $4,587,000,000 (not including administrative costs). Assuming total non-administrative cost of Oregon Medicaid would increase 0.003% with addition of all treatments for gender dysphoria:

HERC staff estimate total cost of adding all treatments for OHP: $100,000-150,000 per year

The Centers for Disease Control and Prevention estimate the average acute medical costs of a single suicide attempt in the United States is $7,234.

Assuming a reduction in suicide attempts from approximately 30% to 8% among OHP patients with gender dysphoria and assuming the total number of patients with gender dysphoria on OHP is 100, and assuming a suicide attempt rate in this population of 2% a year (based on De Cuypere data), we could expect to reduce the number of total suicide attempts from 2 a year to 0.5 per year.

HERC staff estimate of cost savings from reduced suicide attempts with treatment of about $10,000

Overall HERC staff summary:
Treatment of gender dysphoria with cross-sex hormone therapy, gender reassignment surgery or a combination of these treatments results in a significant reduction in depression, anxiety, and suicide attempts. Data from a limited number of studies indicates that a significant reduction in psychiatric symptoms can be obtained from hormone therapy alone; however, the reduction in suicide attempts was shown in studies with a combination of these therapies. The cost of adding cross-sex hormone treatment for gender dysphoria would likely be minimal to the OHP program. The cost of adding gender reassignment surgery would be higher than that of cross-sex hormone therapy alone, but still very low.

CPT codes for sex reassignment surgery

CPT code	Code description	Current placement
19301-19304	Mastectomy	195 CANCER OF BREAST
53430	Urethroplasty, reconstruction of female urethra	91 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM 331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
54125	Amputation of penis; complete	262 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS

CPT code	Code description	Current placement
54400-54417	Insertion/repair/removal of penile prosthesis	529 SEXUAL DYSFUNCTION Some on 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
54520	Orchiectomy, simple (including subcapsular), with or without testicular prosthesis, scrotal or inguinal approach	98,116,211,249,262,331,333,474
54660	Insertion of testicular prosthesis (separate procedure)	98 UNDESCENDED TESTICLE 249 TORSION OF TESTIS
54690	Laparoscopy, surgical; orchiectomy	98,116,428,474
55175-55180	Scrotoplasty	91, 262, 438 HYPOSPADIAS AND EPISPADIAS
55970	Intersex surgery; male to female	Excluded
55980	Intersex surgery; female to male	Excluded
56625	Vulvectomy simple; complete	291 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS
56800	Plastic repair of introitus	125,211,356,428
56805	Clitoroplasty for intersex state	428 ADRENOGENITAL DISORDERS,638 BENIGN CERVICAL CONDITIONS
56810	Perineoplasty, repair of perineum, nonobstetrical	125 ABUSE AND NEGLECT,428, 471 UTERINE PROLAPSE; CYSTOCELE
57106-57107	Vaginectomy, partial removal of vaginal wall;	291,471
57110-57111	Vaginectomy, complete removal of vaginal wall	291
57291-57292	Construction of artificial vagina	356 STRUCTURAL CAUSES OF AMENORRHEA
57335	Vaginoplasty for intersex state	428
58150, 58180, 58260-58262, 58275-58291, 58541-58544, 58550-58554, 58570-58573	Hysterectomy	Multiple lines, with several guidelines
58661	Laparoscopy, surgical; with removal of adnexal structures	Multiple lines
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral	Multiple lines

Note: Rhinoplasty, face-lifting, lip enhancement, facial bone reduction, blepharoplasty, breast augmentation, liposuction of the waist (body contouring), reduction thyroid chondroplasty, hair removal, voice modification surgery (laryngoplasty or shortening of the vocal cords), and skin resurfacing, which have been used in feminization, are considered cosmetic. Similarly, chin implants, nose implants, and lip reduction, which have been used to assist masculinization, are considered cosmetic.

HSC Staff Recommendations:

1) Add cross-sex hormone therapy and sex-reassignment surgery to line 413
    1) Good evidence found for reduction in psychiatric symptoms and suicide attempts with treatment
    2) Overall cost for full spectrum of treatment expected to be minimal, with some cost savings with reduced suicide attempts, psychiatric care, etc.
    3) Add surgical codes as shown below
        i. Advise DMAP to remove CPT 55970 and 55980 from the Excluded List.
    4) Reprioritize line 413 as a category 6 as shown below
    5) Change the guideline for line 413 as shown below

Line 413
Condition: GENDER DYSPHORIA
Treatment: ~~MEDICAL/PSYCHOTHERAPY~~ MEDICAL AND SURGICAL TREATMENT; PSYCHOTHERAPY
ICD-9: 302.85 (Gender identity disorder in adolescents or adults)
ICD10: F64.1-F64.9 (Gender identity disorder)
CPT: 19301-19304, 53430, 54125, 54400-54417, 54520, 54660, 54690, 55175-55180, 55970, 55980, 56625, 56800, 56805, 56810, 57106-57107, 57110-57111, 57291-57292, 57335, 58150, 58180, 58260-58262, 58275-58291, 58541-58544, 58550-58554, 58570-58573, 58661, 58720, 90785,90832-90840, 90846-90853,90882,90887,96101,98966-98969,99051,99060,99070, 99078,99201-99215,99281-99285,99341-99355,99358-99378,99381-99404,99408-99412,99429-99449,99487-99496,99605-99607
HCPCS:G0176,G0177,G0396,G0397,G0459,G0463,H0004,H0023,H0032,H0034, H0035,H2010,H2011,H2014,H2027,H2032,H2033,S9484,T1016

Scoring proposal (current scoring for line 413 in parentheses)
Category: 6 (7)
HL: 3 (3)
Suffering: 4 (4)
Population effects: 0 (0)
Vulnerable population: 0 (0)
Tertiary prevention: 3 (3)
Effectiveness: 2 (2)
Need for service: 1 (1)
Net cost: 2 (2)
Score: 800
Approximate line placement: 349

GUIDELINE XXX GENDER DYSPHORIA

Line 413

Hormone treatment is included on this line for use in delaying the onset of puberty and/or continued pubertal development with GnRH analogues for gender questioning children and adolescents. This therapy should be initiated at the first physical changes of puberty, confirmed by pubertal levels of estradiol or testosterone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria, and must have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.

Cross-sex hormone therapy is included on this line for treatment of adolescents and adults with gender dysphoria who meet appropriate eligibility and readiness criteria. To qualify for cross-sex hormone therapy, the patient must:

1) have persistent, well-documented gender dysphoria
2) have the capacity to make a fully informed decision and to give consent for treatment
3) If significant medical or mental concerns are present, they must be reasonably well controlled
4) have a thorough psychosocial assessment by a qualified mental health professional

Sex reassignment surgery is included for patients who are sufficiently physically fit and meet eligibility criteria. To qualify for surgery, the patient must:

1) Have persistent, well documented gender dysphoria
2) Have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual
3) Have completed twelve months of living in a gender role that is congruent with their gender identity
4) Be 18 years of age or older
5) Have any significant medical or mental health concerns reasonably well controlled
6) have two referrals from qualified mental health professionals who have independently assessed the patient

Prevalence of Gender Identity Disorder and Suicide Risk Among Transgender Veterans Utilizing Veterans Health Administration Care

John R. Blosnich, PhD, George R. Brown, MD, Jillian C. Shipherd, PhD, Michael Kauth, PhD, Rebecca I. Piegari, MS, and Robert M. Bossarte, PhD

Objectives. We estimated the prevalence and incidence of gender identity disorder (GID) diagnoses among veterans in the Veterans Health Administration (VHA) health care system and examined suicide risk among veterans with a GID diagnosis.

Methods. We examined VHA electronic medical records from 2000 through 2011 for 2 official ICD-9 diagnosis codes that indicate transgender status. We generated annual period prevalence estimates and calculated incidence using the prevalence of GID at 2000 as the baseline year. We cross-referenced GID cases with available data (2009–2011) of suicide-related events among all VHA users to examine suicide risk.

Results. GID prevalence in the VHA is higher (22.9/100 000 persons) than are previous estimates of GID in the general US population (4.3/100 000 persons). The rate of suicide-related events among GID-diagnosed VHA veterans was more than 20 times higher than were rates for the general VHA population.

Conclusions. The prevalence of GID diagnosis nearly doubled over 10 years among VHA veterans. Research is needed to examine suicide risk among transgender veterans and how their VHA utilization may be enhanced by new VA initiatives on transgender care. (*Am J Public Health.* 2013;103:e27–e32. doi: 10.2105/AJPH.2013.301507)

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) defines gender identity disorder (GID) as having deeply rooted feelings of persistent discomfort with one's current biological gender and having the desire to be of the opposite gender to the extent that "the disturbance causes clinically significant distress or impairment in . . . important areas of functioning."[1(p260)]

Although the diagnosis is relatively rare, persons diagnosed with GID constitute a subpopulation of people who experience numerous disparities in physical and mental health as well as health care access.[2] Although a precise estimate of GID occurrence among the general population is unknown, one theoretical framework (i.e., flight into hypermasculinity) posits that GID may be overrepresented in the military and among veterans,[3] and there is support for this hypothesis in community-based samples of transgender persons in which high prevalence of military service is observed.[4] Furthermore, there is evidence of elevated risk for suicidal behavior among transgender populations.[5–10] However, prevalence of GID and suicide-related events (e.g., suicide planning, suicide attempt) have yet to be examined among veterans who have received Veterans Health Administration (VHA) services. We have addressed this unmet need.

GENDER IDENTITY DISORDER TERMINOLOGY

Although there are multiple ways that a person diagnosed with GID may self-identify, the 2 common terms used in the literature for this self-identification are transgender and transsexual. Transgender is a term with broader scope; it typically encompasses individuals who self-identify as being or living outside socially constructed gender roles of masculinity and femininity. Transsexual is often used to conceptualize a subset of transgender persons who usually desire to undergo physical changes to their bodies, potentially including cross-gender hormone treatments and gender reassignment surgery.[11]

Because the data for our analysis did not permit an assessment of self-identified transgender or transsexual status, we have used the terms GID, transgender, and transsexual interchangeably, and our review of the literature includes findings of studies with GID, transgender, and transsexual samples. Although these populations share many qualities, we duly note that persons with GID constitute only a portion of transgender and transsexual communities. Thus, our focus on persons diagnosed with GID (i.e., a clinical subpopulation) should not be misinterpreted to represent either transgender or transsexual populations at large.

Currently, the most common treatments for GID are combinations of psychotherapy, cross-gender hormone therapy, living full time in the cross-gender role, electrolysis, voice therapy, and surgical procedures.[12–14]

PREVALENCE OF GENDER IDENTITY DISORDER

Precise estimates of the number of persons with GID are difficult to make, as not every person with GID is able to access care from a health care provider who is knowledgeable in this diagnosis.[5,15,16] Moreover, many studies of GID use records of gender reassignment surgeries as a proxy census (i.e., counting only transsexuals with severe forms of GID),[17] which likely produces underestimates of GID prevalence, as only a small fraction of GID-diagnosed individuals undergoes gender reassignment surgeries.[18]

The *DSM-IV* estimates that 1 in 30 000 natal males and 1 in 100 000 natal females have GID among the US population; however, these figures are based on older, limited data.[1] More recent research, from other countries,

Effects of Different Steps in Gender Reassignment Therapy on Psychopathology: A Prospective Study of Persons with a Gender Identity Disorder

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DOI: 10.1111/jsm.12363

ABSTRACT

Introduction. At the start of gender reassignment therapy, persons with a gender identity disorder (GID) may deal with various forms of psychopathology. Until now, a limited number of publications focus on the effect of the different phases of treatment on this comorbidity and other psychosocial factors.

Aims. The aim of this study was to investigate how gender reassignment therapy affects psychopathology and other psychosocial factors.

Methods. This is a prospective study that assessed 57 individuals with GID by using the Symptom Checklist-90 (SCL-90) at three different points of time: at presentation, after the start of hormonal treatment, and after sex reassignment surgery (SRS). Questionnaires on psychosocial variables were used to evaluate the evolution between the presentation and the postoperative period. The data were statistically analyzed by using SPSS 19.0, with significance levels set at $P < 0.05$.

Main Outcome Measures. The psychopathological parameters include overall psychoneurotic distress, anxiety, agoraphobia, depression, somatization, paranoid ideation/psychoticism, interpersonal sensitivity, hostility, and sleeping problems. The psychosocial parameters consist of relationship, living situation, employment, sexual contacts, social contacts, substance abuse, and suicide attempt.

Results. A difference in SCL-90 overall psychoneurotic distress was observed at the different points of assessments ($P = 0.003$), with the most prominent decrease occurring after the initiation of hormone therapy ($P < 0.001$). Significant decreases were found in the subscales such as anxiety, depression, interpersonal sensitivity, and hostility. Furthermore, the SCL-90 scores resembled those of a general population after hormone therapy was initiated. Analysis of the psychosocial variables showed no significant differences between pre- and postoperative assessments.

Conclusions. A marked reduction in psychopathology occurs during the process of sex reassignment therapy, especially after the initiation of hormone therapy. **Heylens G, Verroken C, De Cock S, T'Sjoen G, and De Cuypere G. Reassignment therapy on psychopathology: A prospective study of persons with a gender identity disorder. J Sex Med 2014;11:119–126.**

Key Words. Gender Reassignment Therapy; Psychopathology; Gender Identity Disorder; Gender Dysphoria

Introduction

According to the DSM-IV-R classification, transsexualism or gender identity disorder (GID) is an extreme form of gender dysphoria characterized by a strong and persistent identification with the opposite sex. It is accompanied by the wish to get rid of one's own primary and secondary sex characteristics and to live completely as someone from the opposite sex [1]. In Belgium, the prevalence is around 7.75 male-to-female (MtF) and 2.96 female-to-male (FtM) per 100,000, which is similar to other Western European countries [2].

The etiology of transsexualism remains unclear. Besides biological factors, such as hormonal

Psychoneuroendocrinology (2014) 39, 65—73

Available online at www.sciencedirect.com

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Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: Results from a longitudinal study

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Received 7 August 2013; received in revised form 11 September 2013; accepted 30 September 2013

KEYWORDS
Transsexualism;
Hormonal sex-reassignment therapy;
Anxiety;
Depression;
Mental Health;
Psychiatric comorbidity;
Functional impairment;
Subthreshold psychiatric symptoms

Summary The aim of the present study was to evaluate the presence of psychiatric diseases/symptoms in transsexual patients and to compare psychiatric distress related to the hormonal intervention in a one year follow-up assessment. We investigated 118 patients before starting the hormonal therapy and after about 12 months. We used the SCID-I to determine major mental disorders and functional impairment. We used the Zung Self-Rating Anxiety Scale (SAS) and the Zung Self-Rating Depression Scale (SDS) for evaluating self-reported anxiety and depression. We used the Symptom Checklist 90-R (SCL-90-R) for assessing self-reported global psychological symptoms. Seventeen patients (14%) had a DSM-IV-TR axis I psychiatric comorbidity. At enrollment the mean SAS score was above the normal range. The mean SDS and SCL-90-R scores were on the normal range except for SCL-90-R anxiety subscale. When treated, patients reported lower SAS, SDS and SCL-90-R scores, with statistically significant differences. Psychiatric distress and functional impairment were present in a significantly higher percentage of patients before starting the hormonal treatment than after 12 months (50% vs. 17% for anxiety; 42% vs. 23% for depression; 24% vs. 11% for psychological symptoms; 23% vs. 10% for functional impairment). The results revealed that the majority of transsexual patients have no psychiatric comorbidity, suggesting that transsexualism is not necessarily associated with severe comorbid psychiatric findings. The condition, however, seemed to be associated with subthreshold anxiety/depression, psychological symptoms and functional impairment. Moreover, treated patients reported less psychiatric distress. Therefore, hormonal treatment seemed to have a positive effect on transsexual patients' mental health.

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0306-4530/$ — see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psyneuen.2013.09.029

OPEN ACCESS Freely available online

PLoS one

Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden

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Abstract

Context: The treatment for transsexualism is sex reassignment, including hormonal treatment and surgery aimed at making the person's body as congruent with the opposite sex as possible. There is a dearth of long term, follow-up studies after sex reassignment.

Objective: To estimate mortality, morbidity, and criminal rate after surgical sex reassignment of transsexual persons.

Design: A population-based matched cohort study.

Setting: Sweden, 1973-2003.

Participants: All 324 sex-reassigned persons (191 male-to-females, 133 female-to-males) in Sweden, 1973–2003. Random population controls (10:1) were matched by birth year and birth sex or reassigned (final) sex, respectively.

Main Outcome Measures: Hazard ratios (HR) with 95% confidence intervals (CI) for mortality and psychiatric morbidity were obtained with Cox regression models, which were adjusted for immigrant status and psychiatric morbidity prior to sex reassignment (adjusted HR [aHR]).

Results: The overall mortality for sex-reassigned persons was higher during follow-up (aHR 2.8; 95% CI 1.8–4.3) than for controls of the same birth sex, particularly death from suicide (aHR 19.1; 95% CI 5.8–62.9). Sex-reassigned persons also had an increased risk for suicide attempts (aHR 4.9; 95% CI 2.9–8.5) and psychiatric inpatient care (aHR 2.8; 95% CI 2.0–3.9). Comparisons with controls matched on reassigned sex yielded similar results. Female-to-males, but not male-to-females, had a higher risk for criminal convictions than their respective birth sex controls.

Conclusions: Persons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population. Our findings suggest that sex reassignment, although alleviating gender dysphoria, may not suffice as treatment for transsexualism, and should inspire improved psychiatric and somatic care after sex reassignment for this patient group.

Citation: Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Långström N, et al. (2011) Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. PLoS ONE 6(2): e16885. doi:10.1371/journal.pone.0016885

Editor: James Scott, The University of Queensland, Australia

Received September 30, 2010; **Accepted** January 9, 2011; **Published** February 22, 2011

Funding: Financial support was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and the Karolinska Institutet, and through grants from the Swedish Medical Research Council (K2008-62x-14647-06-3) and the Royal Swedish Academy of Sciences (Torsten Amundson's Foundation). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and the final responsibility for the decision to submit for publication was made by the corresponding author.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Transsexualism (ICD-10),[1] or gender identity disorder (DSM-IV),[2] is a condition in which a person's gender identity - the sense of being a man or a woman - contradicts his or her bodily sex characteristics. The individual experiences gender dysphoria and desires to live and be accepted as a member of the opposite sex.

The treatment for transsexualism includes removal of body hair, vocal training, and cross-sex hormonal treatment aimed at making the person's body as congruent with the opposite sex as possible to alleviate the gender dysphoria. Sex reassignment also involves the surgical removal of body parts to make external sexual characteristics resemble those of the opposite sex, so called sex reassignment/confirmation surgery (SRS). This is a unique

intervention not only in psychiatry but in all of medicine. The present form of sex reassignment has been practised for more than half a century and is the internationally recognized treatment to ease gender dysphoria in transsexual persons.[3,4]

Despite the long history of this treatment, however, outcome data regarding mortality and psychiatric morbidity are scant. With respect to suicide and deaths from other causes after sex reassignment, an early Swedish study followed 24 transsexual persons for an average of six years and reported one suicide.[5] A subsequent Swedish study recorded three suicides after sex reassignment surgery of 175 patients.[6] A recent Swedish follow-up study reported no suicides in 60 transsexual patients, but one death due to complications after the sex reassignment surgery.[7] A Danish study reported death by suicide in 3 out of 29 operated male-to-female transsexual persons followed for an average of six years.[8] By contrast, a Belgian study of 107 transsexual persons followed for 4–6 years found no suicides or deaths from other causes.[9] A large Dutch single-centre study (N = 1,109), focusing on adverse events following hormonal treatment, compared the outcome after cross-sex hormone treatment with national Dutch standardized mortality and morbidity rates and found no increased mortality, with the exception of death from suicide and AIDS in male-to-females 25–39 years of age.[10] The same research group concluded in a recent report that treatment with cross-sex hormones seems acceptably safe, but with the reservation that solid clinical data are missing.[11] A limitation with respect to the Dutch cohort is that the proportion of patients treated with cross-sex hormones who also had surgical sex-reassignment is not accounted for.[10]

Data is inconsistent with respect to psychiatric morbidity post sex reassignment. Although many studies have reported psychiatric and psychological improvement after hormonal and/or surgical treatment,[7,12,13,14,15,16] other have reported on regrets,[17] psychiatric morbidity, and suicide attempts after SRS.[9,18] A recent systematic review and meta-analysis concluded that approximately 80% reported subjective improvement in terms of gender dysphoria, quality of life, and psychological symptoms, but also that there are studies reporting high psychiatric morbidity and suicide rates after sex reassignment.[19] The authors concluded though that the evidence base for sex reassignment "is of very low quality due to the serious methodological limitations of included studies."

The methodological shortcomings have many reasons. First, the nature of sex reassignment precludes double blind randomized controlled studies of the result. Second, transsexualism is rare [20] and many follow-ups are hampered by small numbers of subjects.[5,8,21,22,23,24,25,26,27,28] Third, many sex reassigned persons decline to participate in follow-up studies, or relocate after surgery, resulting in high drop-out rates and consequent selection bias.[6,9,12,21,24,28,29,30] Forth, several follow-up studies are hampered by limited follow-up periods.[7,9,21,22,26,30] Taken together, these limitations preclude solid and generalisable conclusions. A long-term population-based controlled study is one way to address these methodological shortcomings.

Here, we assessed mortality, psychiatric morbidity, and psychosocial integration expressed in criminal behaviour after sex reassignment in transsexual persons, in a total population cohort study with long-term follow-up information obtained from Swedish registers. The cohort was compared with randomly selected population controls matched for age and gender. We adjusted for premorbid differences regarding psychiatric morbidity and immigrant status. This study design sheds new light on transsexual persons' health after sex reassignment. It does not, however, address whether sex reassignment is an effective treatment or not.

Methods

National registers

The study population was identified by the linkage of several Swedish national registers, which contained a total of 13.8 million unique individuals. The Hospital Discharge Register (HDR, held by the National Board of Health and Welfare) contains discharge diagnoses, up to seven contributory diagnoses, external causes of morbidity or mortality, surgical procedure codes, and discharge date. Discharge diagnoses are coded according to the 8th (1969-1986), 9th (1987–1996), and 10th editions (1997-) of the International Classification of Diseases (ICD). The register covers virtually all psychiatric inpatient episodes in Sweden since 1973. Discharges that occurred up to 31 December 2003 were included. Surgical procedure codes could not be used for this study due to the lack of a specific code for sex reassignment surgery. The Total Population Register (TPR, held by Statistics Sweden) is comprised of data about the entire Swedish population. Through linkage with the Total Population Register it was possible to identify birth date and birth gender for all study subjects. The register is updated every year and gender information was available up to 2004/2005. The Medical Birth Register (MBR) was established in 1973 and contains birth data, including gender of the child at birth. National censuses based on mandatory self-report questionnaires completed by all adult citizens in 1960, 1970, 1980, and 1990 provided information on individuals, households, and dwellings, including gender, living area, and highest educational level. Complete migration data, including country of birth for immigrants for 1969–2003, were obtained from the TPR. In addition to educational information from the censuses, we also obtained highest educational level data for 1990 and 2000 from the Register of Education. The Cause of Death Register (CDR, Statistics Sweden) records all deaths in Sweden since 1952 and provided information on date of death and causes of death. Death events occurring up to 31 December 2003 are included in the study. The Crime Register (held by the National Council of Crime Prevention) provided information regarding crime type and date on all criminal convictions in Sweden during the period 1973–2004. Attempted and aggravated forms of all offences were also included. All crimes in Sweden are registered regardless of insanity at the time of perpetration; for example, for individuals who suffered from psychosis at the time of the offence. Moreover, conviction data include individuals who received custodial or non-custodial sentences and cases where the prosecutor decided to caution or fine without court proceedings. Finally, Sweden does not differ considerably from other members of the European Union regarding rates of violent crime and their resolution.[31]

Study population, identification of sex-reassigned persons (exposure assessment)

The study was designed as a population-based matched cohort study. We used the individual national registration number, assigned to all Swedish residents, including immigrants on arrival, as the primary key through all linkages. The registration number consists of 10 digits; the first six provide information of the birth date, whereas the ninth digit indicates the gender. In Sweden, a person presenting with gender dysphoria is referred to one of six specialised gender teams that evaluate and treat patients principally according to international consensus guidelines: Standards of Care.[3] With a medical certificate, the person applies to the National Board of Health and Welfare to receive permission for sex reassignment surgery and a change of legal sex status. A new national registration number signifying the new gender is assigned after sex reassignment surgery. The National

Board of Health and Welfare maintains a link between old and new national registration numbers, making it possible to follow individuals undergoing sex reassignment across registers and over time. Hence, sex reassignment surgery in Sweden requires (i) a transsexualism diagnosis and (ii) permission from the National Board of Health and Welfare.

A person was defined as exposed to sex reassignment surgery if two criteria were met: (i) at least one inpatient diagnosis of gender identity disorder diagnosis without concomitant psychiatric diagnoses in the Hospital Discharge Register, and (ii) at least one discrepancy between gender variables in the Medical Birth Register (from 1973 and onwards) or the National Censuses from 1960, 1970, 1980, or 1990 and the latest gender designation in the Total Population Register. The first criterion was employed to capture the hospitalization for sex reassignment surgery that serves to secure the diagnosis and provide a time point for sex reassignment surgery; the plastic surgeons namely record the reason for sex reassignment surgery, i.e., transsexualism, but not any co-occurring psychiatric morbidity. The second criterion was used to ensure that the person went through all steps in sex-reassignment and also changed sex legally.

The date of sex reassignment (start of follow-up) was defined as the first occurrence of a gender identity disorder diagnosis, without any other concomitant psychiatric disorder, in the Hospital Discharge Register after the patient changed sex status (any discordance in sex designation across the Censuses, Medical Birth, and Total Population registers). If this information was missing, we used instead the closest date in the Hospital Discharge Register on which the patient was diagnosed with gender identity disorder without concomitant psychiatric disorder prior to change in sex status. The reason for prioritizing the use of a gender identity disorder diagnosis *after* changed sex status over *before* was to avoid overestimating person-years at risk of sex-reassigned person.

Using these criteria, a total of 804 patients with gender identity disorder were identified, whereof 324 displayed a shift in the gender variable during the period 1973–2003. The 480 persons that did not shift gender variable comprise persons who either did not apply, or were not approved, for sex reassignment surgery. Moreover, the ICD 9 code 302 is a non specific code for sexual disorders. Hence, this group might also comprise persons that were hospitalized for sexual disorders other than transsexualism. Therefore, they were omitted from further analyses. Of the remaining 324 persons, 288 were identified with the gender identity diagnosis *after* and 36 *before* change of sex status. Out of the 288 persons identified *after* changed sex status, 185 could also be identified *before* change in sex status. The median time lag between the hospitalization *before* and *after* sex change for these 185 persons was 0.96 years (mean 2.2 years, SD 3.3).

Gender identity disorder was coded according to ICD-8: 302.3 (transsexualism) and 302.9 (sexual deviation NOS); ICD-9: 302 (overall code for sexual deviations and disorders, more specific codes were not available in ICD-9); and ICD-10: F64.0 (transsexualism), F64.1 (dual-role transvestism), F64.8 (other gender identity disorder), and F64.9 (gender identity disorder NOS). Other psychiatric disorders were coded as ICD-8: 290-301 and 303-315; ICD-9: 290-301 and 303-319; and ICD-10: F00-F63 as well as F65-F99.

Identification of population-based controls (unexposed group)

For each exposed person (N = 324), we randomly selected 10 unexposed controls. A person was defined as unexposed if there were no discrepancies in sex designation across the Censuses, Medical Birth, and Total Population registers *and* no gender identity disorder diagnosis according to the Hospital Discharge Register. Control persons were matched by sex and birth year and had to be alive and residing in Sweden at the estimated sex reassignment date of the case person. To study possible gender-specific effects on outcomes of interest, we used two different control groups: one with the same sex as the case individual at birth (birth sex matching) and the other with the sex that the case individual had been reassigned to (final sex matching).

Outcome measures

We studied mortality, psychiatric morbidity, accidents, and crime following sex reassignment. More specifically, we investigated: (1) all-cause mortality, (2) death by definite/uncertain suicide, (3) death by cardiovascular disease, and (4) death by tumour. Morbidity included (5) any psychiatric disorder (gender identity disorders excluded), (6) alcohol/drug misuse and dependence, (7) definite/uncertain suicide attempt, and (8) accidents. Finally, we addressed court convictions for (9) any criminal offence and (10) any violent offence. Each individual could contribute with several outcomes, but only one event per outcome. Causes of death (Cause of Death Registry from 1952 and onwards) were defined according to ICD as suicide (ICD-8 and ICD-9 codes E950-E959 and E980-E989, ICD-10 codes X60-X84 and Y10-Y34); cardiovascular disease (ICD-8 codes 390-458, ICD-9 codes 390-459, ICD-10 codes I00-I99); neoplasms (ICD-8 and ICD-9 codes 140-239, ICD-10 codes C00-D48), any psychiatric disorder (gender identity disorders excluded); (ICD-8 codes 290-301 and 303-315, ICD-9 codes 290-301 and 303-319, ICD-10 codes F00-F63 and F65-F99); alcohol/drug abuse and dependence (ICD-8 codes 303-304, ICD-9 codes 303-305 (tobacco use disorder excluded), ICD-10 codes F10-F16 and F18-F19 (x5 excluded); and accidents (ICD-8 and ICD-9 codes E800-E929, ICD-10 codes V01-X59).

Any criminal conviction during follow-up was counted; specifically, violent crime was defined as homicide and attempted homicide, aggravated assault and assault, robbery, threatening behaviour, harassment, arson, or any sexual offense.[32]

Covariates

Severe psychiatric morbidity was defined as inpatient care according to ICD-8 codes 291, 295-301, 303-304, and 307; ICD-9 codes 291-292, 295-298, 300-301, 303-305 (tobacco use disorder excluded), 307.1, 307.5, 308-309, and 311; ICD-10 codes F10-F16, F18-F25, F28-F45, F48, F50, and F60-F62. Immigrant status, defined as individuals born abroad, was obtained from the Total Population Register. All outcome/covariate variables were dichotomized (i.e., affected or unaffected) and without missing values.

Statistical analyses

Each individual contributed person-time from study entry (for exposed: date of sex reassignment; for unexposed: date of sex reassignment of matched case) until date of outcome event, death, emigration, or end of study period (31 December 2003), whichever came first. The association between exposure (sex reassignment) and outcome (mortality, morbidity, crime) was measured by hazard ratios (HR) with 95% CIs, taking follow-up time into account. HRs were estimated from Cox proportional hazard regression models, stratified on matched sets (1:10) to account for the matching by sex, age, and calendar time (birth year). We present crude HRs (though adjusted for sex and age through matching) and confounder-adjusted HRs [aHRs] for all outcomes. The two potential confounders, immigrant status (yes/no) and history of severe psychiatric morbidity (yes/no) prior to sex

reassignment, were chosen based on previous research[18,33] and different prevalence across cases and controls (Table 1).

Gender-separated analyses were performed and a Kaplan-Meier survival plot graphically illustrates the survival of the sex reassigned cohort and matched controls (all-cause mortality) over time. The significance level was set at 0.05 (all tests were two-sided). All outcome/covariate variables were without missing values, since they are generated from register data, which are either present (affected) or missing (unaffected). The data were analysed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Ethics

The data linking of national registers required for this study was approved by the IRB at Karolinska Institutet, Stockholm. All data were analyzed anonymously; therefore, informed consent for each individual was neither necessary nor possible.

Results

We identified 324 transsexual persons (exposed cohort) who underwent sex reassignment surgery and were assigned a new legal sex between 1973 and 2003. These constituted the sex-reassigned (exposed) group. Fifty-nine percent (N = 191) of sex-reassigned persons were male-to-females and 41% (N = 133) female-to-males, yielding a sex ratio of 1.4:1 (Table 1).

The average follow-up time for all-cause mortality was 11.4 (median 9.1) years. The average follow-up time for the risk of being hospitalized for any psychiatric disorder was 10.4 (median 8.1).

Characteristics prior to sex reassignment

Table 1 displays demographic characteristics of sex-reassigned and control persons prior to study entry (sex reassignment). There were no substantial differences between female-to-males and male-to-females regarding measured baseline characteristics. Immigrant status was twice as common among transsexual individuals compared to controls, living in an urban area somewhat more common, and higher education about equally prevalent. Transsexual individuals had been hospitalized for psychiatric morbidity other than gender identity disorder prior to sex reassignment about four times more often than controls. To adjust for these baseline discrepancies, hazard ratios adjusted for immigrant status and psychiatric morbidity prior to baseline are presented for all outcomes [aHRs].

Mortality

Table 2 describes the risks for selected outcomes during follow-up among sex-reassigned persons, compared to same-age controls of the same birth sex. Sex-reassigned transsexual persons of both genders had approximately a three times higher risk of all-cause mortality than controls, also after adjustment for covariates. Table 2

Table 1. Baseline characteristics among sex-reassigned subjects in Sweden (N = 324) and population controls matched for birth year and sex.

Characteristic at baseline	Sex-reassigned subjects (N = 324)	Birth-sex matched controls (N = 3,240)	Final-sex matched controls (N = 3,240)
Gender			
Female at birth, male after sex change	133 (41%)	1,330 (41%)	1,330 (41%)
Male at birth, female after sex change	191 (59%)	1,910 (59%)	1,910 (59%)
Average age at study entry [years] (SD, min-max)			
Female at birth, male after sex change	33.3 (8.7, 20–62)	33.3 (8.7, 20–62)	33.3 (8.7, 20–62)
Male at birth, female after sex change	36.3 (10.1, 21–69)	36.3 (10.1, 21–69)	36.3 (10.1, 21–69)
Both genders	35.1 (9.7, 20–69)	35.1 (9.7, 20–69)	35.1 (9.7, 20–69)
Immigrant status			
Female at birth, male after sex change	28 (21%)	118 (9%)	100 (8%)
Male at birth, female after sex change	42 (22%)	176 (9%)	164 (9%)
Both genders	70 (22%)	294 (9%)	264 (8%)
Less than 10 years of schooling prior to entry vs. 10 years or more			
Females at birth, males after sex change	49 (44%); 62 (56%)	414 (37%); 714 (63%)	407 (36%); 713 (64%)
Males at birth, females after sex change	61 (41%); 89 (59%)	665 (40%); 1,011 (60%)	595 (35%); 1,091 (65%)
All individuals with data	110 (42%); 151 (58%)	1,079 (38%); 1,725 (62%)	1,002 (36%); 1,804 (64%)
Psychiatric morbidity* prior to study entry			
Female at birth, male after sex change	22 (17%)	47 (4%)	42 (3%)
Male at birth, female after sex change	36 (19%)	76 (4%)	72 (4%)
Both genders	58 (18%)	123 (4%)	114 (4%)
Rural [vs. urban] living area prior to entry			
Female at birth, male after sex change	13 (10%)	180 (14%)	195 (15%)
Male at birth, female after sex change	20 (10%)	319 (17%)	272 (14%)
Both genders	33 (10%)	499 (15%)	467 (14%)

Note:
*Hospitalizations for gender identity disorder were not included.
doi:10.1371/journal.pone.0016885.t001

Table 2. Risk of various outcomes among sex-reassigned subjects in Sweden (N = 324) compared to population controls matched for birth year and birth sex.

	Number of events cases/ controls 1973–2003	Outcome incidence rate per 1000 person-years 1973–2003 (95% CI)		Crude hazard ratio (95% CI) 1973–2003	Adjusted* hazard ratio (95% CI) 1973–2003	Adjusted* hazard ratio (95% CI) 1973–1988	Adjusted* hazard ratio (95% CI) 1989–2003
		Cases	Controls				
Any death	27/99	7.3 (5.0–10.6)	2.5 (2.0–3.0)	2.9 (1.9–4.5)	2.8 (1.8–4.3)	3.1 (1.9–5.0)	1.9 (0.7–5.0)
Death by suicide	10/5	2.7 (1.5–5.0)	0.1 (0.1–0.3)	19.1 (6.5–55.9)	19.1 (5.8–62.9)	N/A	N/A
Death by cardiovascular disease	9/42	2.4 (1.3–4.7)	1.1 (0.8–1.4)	2.6 (1.2–5.4)	2.5 (1.2–5.3)	N/A	N/A
Death by neoplasm	8/38	2.2 (1.1–4.3)	1.0 (0.7–1.3)	2.1 (1.0–4.6)	2.1 (1.0–4.6)	N/A	N/A
Any psychiatric hospitalisation‡	64/173	19.0 (14.8–24.2)	4.2 (3.6–4.9)	4.2 (3.1–5.6)	2.8 (2.0–3.9)	3.0 (1.9–4.6)	2.5 (1.4–4.2)
Substance misuse	22/78	5.9 (3.9–8.9)	1.8 (1.5–2.3)	3.0 (1.9–4.9)	1.7 (1.0–3.1)	N/A	N/A
Suicide attempt	29/44	7.9 (5.5–11.4)	1.0 (0.8–1.4)	7.6 (4.7–12.4)	4.9 (2.9–8.5)	7.9 (4.1–15.3)	2.0 (0.7–5.3)
Any accident	32/233	9.0 (6.3–12.7)	5.7 (5.0–6.5)	1.6 (1.1–2.3)	1.4 (1.0–2.1)	1.6 (1.0–2.5)	1.1 (0.5–2.2)
Any crime	60/350	18.5 (14.3–23.8)	9.0 (8.1–10.0)	1.9 (1.4–2.5)	1.3 (1.0–1.8)	1.6 (1.1–2.4)	0.9 (0.6–1.5)
Violent crime	14/61	3.6 (2.1–6.1)	1.4 (1.1–1.8)	2.7 (1.5–4.9)	1.5 (0.8–3.0)	N/A	N/A

Notes:
*Adjusted for psychiatric morbidity prior to baseline and immigrant status.
‡Hospitalisations for gender identity disorder were excluded.
N/A Not applicable due to sparse data.
doi:10.1371/journal.pone.0016885.t002

separately lists the outcomes depending on when sex reassignment was performed: during the period 1973-1988 or 1989–2003. Even though the overall mortality was increased across both time periods, it did not reach statistical significance for the period 1989–2003. The Kaplan-Meier curve (Figure 1) suggests that survival of transsexual persons started to diverge from that of matched controls after about 10 years of follow-up. The cause-specific mortality from suicide was much higher in sex-reassigned persons, compared to matched controls. Mortality due to cardiovascular disease was moderately increased among the sex-reassigned, whereas the numerically increased risk for malignancies was borderline statistically significant. The malignancies were lung cancer (N = 3), tongue cancer (N = 1), pharyngeal cancer (N = 1), pancreas cancer (N = 1), liver cancer (N = 1), and unknown origin (N = 1).

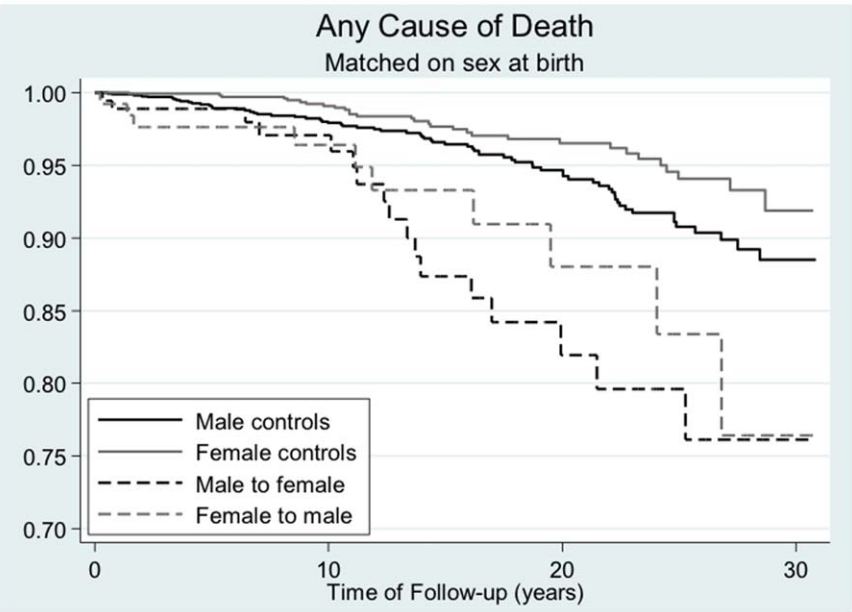

Figure 1. Death from any cause as a function of time after sex reassignment among 324 transsexual persons in Sweden (male-to-female: N = 191, female-to-male: N = 133), and population controls matched on birth year.
doi:10.1371/journal.pone.0016885.g001

Psychiatric morbidity, substance misuse, and accidents

Sex-reassigned persons had a higher risk of inpatient care for a psychiatric disorder other than gender identity disorder than controls matched on birth year and birth sex (Table 2). This held after adjustment for prior psychiatric morbidity, and was true regardless of whether sex reassignment occurred before or after 1989. In line with the increased mortality from suicide, sex-reassigned individuals were also at a higher risk for suicide attempts, though this was not statistically significant for the time period 1989–2003. The risks of being hospitalised for substance misuse or accidents were not significantly increased after adjusting for covariates (Table 2).

Crime rate

Transsexual individuals were at increased risk of being convicted for any crime or violent crime after sex reassignment (Table 2); this was, however, only significant in the group who underwent sex reassignment before 1989.

Gender differences

Comparisons of female-to-males and male-to-females, although hampered by low statistical power and associated wide confidence intervals, suggested mostly similar risks for adverse outcomes (Tables S1 and S2). However, violence against self (suicidal behaviour) and others ([violent] crime) constituted important exceptions. First, male-to-females had significantly increased risks for suicide attempts compared to both female (aHR 9.3; 95% CI 4.4–19.9) and male (aHR 10.4; 95% CI 4.9–22.1) controls. By contrast, female-to-males had significantly increased risk of suicide attempts only compared to male controls (aHR 6.8; 95% CI 2.1–21.6) but not compared to female controls (aHR 1.9; 95% CI 0.7–4.8). This suggests that male-to-females are at higher risk for suicide attempts after sex reassignment, whereas female-to-males maintain a female pattern of suicide attempts after sex reassignment (Tables S1 and S2).

Second, regarding any crime, male-to-females had a significantly increased risk for crime compared to female controls (aHR 6.6; 95% CI 4.1–10.8) but not compared to males (aHR 0.8; 95% CI 0.5–1.2). This indicates that they retained a male pattern regarding criminality. The same was true regarding violent crime. By contrast, female-to-males had higher crime rates than female controls (aHR 4.1; 95% CI 2.5–6.9) but did not differ from male controls. This indicates a shift to a male pattern regarding criminality and that sex reassignment is coupled to increased crime rate in female-to-males. The same was true regarding violent crime.

Discussion

Principal findings and comparison with previous research

We report on the first nationwide population-based, long-term follow-up of sex-reassigned transsexual persons. We compared our cohort with randomly selected population controls matched for age and gender. The most striking result was the high mortality rate in both male-to-females and female-to males, compared to the general population. This contrasts with previous reports (with one exception[8]) that did not find an increased mortality rate after sex reassignment, or only noted an increased risk in certain subgroups.[7,9,10,11] Previous clinical studies might have been biased since people who regard their sex reassignment as a failure are more likely to be lost to follow-up. Likewise, it is cumbersome to track deceased persons in clinical follow-up studies. Hence, population-based register studies like the present are needed to improve representativity.[19,34]

The poorer outcome in the present study might also be explained by longer follow-up period (median >10 years) compared to previous studies. In support of this notion, the survival curve (Figure 1) suggests increased mortality from ten years after sex reassignment and onwards. In accordance, the overall mortality rate was only significantly increased for the group operated before 1989. However, the latter might also be explained by improved health care for transsexual persons during 1990s, along with altered societal attitudes towards persons with different gender expressions.[35]

Mortality due to cardiovascular disease was significantly increased among sex reassigned individuals, albeit these results should be interpreted with caution due to the low number of events. This contrasts, however, a Dutch follow-up study that reported no increased risk for cardiovascular events.[10,11] A recent meta-analysis concluded, however, that data on cardiovascular outcome after cross-sex steroid use are sparse, inconclusive, and of very low quality.[34]

With respect to neoplasms, prolonged hormonal treatment might increase the risk for malignancies,[36] but no previous study has tested this possibility. Our data suggested that the cause-specific risk of death from neoplasms was increased about twice (borderline statistical significance). These malignancies (see Results), however, are unlikely to be related to cross-hormonal treatment.

There might be other explanations to increased cardiovascular death and malignancies. Smoking was in one study reported in almost 50% by the male-to females and almost 20% by female-to-males.[9] It is also possible that transsexual persons avoid the health care system due to a presumed risk of being discriminated.

Mortality from suicide was strikingly high among sex-reassigned persons, also after adjustment for prior psychiatric morbidity. In line with this, sex-reassigned persons were at increased risk for suicide attempts. Previous reports [6,8,10,11] suggest that transsexualism is a strong risk factor for suicide, also after sex reassignment, and our long-term findings support the need for continued psychiatric follow-up for persons at risk to prevent this.

Inpatient care for psychiatric disorders was significantly more common among sex-reassigned persons than among matched controls, both before and after sex reassignment. It is generally accepted that transsexuals have more psychiatric ill-health than the general population prior to the sex reassignment.[18,21,22,33] It should therefore come as no surprise that studies have found high rates of depression,[9] and low quality of life[16,25] also after sex reassignment. Notably, however, in this study the increased risk for psychiatric hospitalisation persisted even after adjusting for psychiatric hospitalisation prior to sex reassignment. This suggests that even though sex reassignment alleviates gender dysphoria, there is a need to identify and treat co-occurring psychiatric morbidity in transsexual persons not only before but also after sex reassignment.

Criminal activity, particularly violent crime, is much more common among men than women in the general population. A previous study of all applications for sex reassignment in Sweden up to 1992 found that 9.7% of male-to-female and 6.1% of female-to-male applicants had been prosecuted for a crime.[33] Crime after sex reassignment, however, has not previously been studied. In this study, male-to-female individuals had a higher risk for criminal convictions compared to female controls but not compared to male controls. This suggests that the sex reassignment procedure neither increased nor decreased the risk for criminal offending in male-to-females. By contrast, female-to-males were at a higher risk for criminal convictions compared to female controls and did not differ from male controls, which suggests increased crime proneness in female-to-males after sex reassignment.

Strengths and limitations of the study

Strengths of this study include nationwide representativity over more than 30 years, extensive follow-up time, and minimal loss to follow-up. Many previous studies suffer from low outcome ascertainment,[6,9,21,29] whereas this study has captured almost the entire population of sex-reassigned transsexual individuals in Sweden from 1973–2003. Moreover, previous outcome studies have mixed pre-operative and post-operative transsexual persons,[22,37] while we included only post-operative transsexual persons that also legally changed sex. Finally, whereas previous studies either lack a control group or use standardised mortality rates or standardised incidence rates as comparisons,[9,10,11] we selected random population controls matched by birth year, and either birth or final sex.

Given the nature of sex reassignment, a double blind randomized controlled study of the result after sex reassignment is not feasible. We therefore have to rely on other study designs. For the purpose of evaluating whether sex reassignment is an effective treatment for gender dysphoria, it is reasonable to compare reported gender dysphoria pre and post treatment. Such studies have been conducted either prospectively[7,12] or retrospectively,[5,6,9,22,25,26,29,38] and suggest that sex reassignment of transsexual persons improves quality of life and gender dysphoria. The limitation is of course that the treatment has not been assigned randomly and has not been carried out blindly.

For the purpose of evaluating the safety of sex reassignment in terms of morbidity and mortality, however, it is reasonable to compare sex reassigned persons with matched population controls. The caveat with this design is that transsexual persons before sex reassignment might differ from healthy controls (although this bias can be statistically corrected for by adjusting for baseline differences). It is therefore important to note that the current study is only informative with respect to transsexuals persons health after sex reassignment; no inferences can be drawn as to the effectiveness of sex reassignment as a treatment for transsexualism. In other words, the results should not be interpreted such as sex reassignment *per se* increases morbidity and mortality. Things might have been even worse without sex reassignment. As an analogy, similar studies have found increased somatic morbidity, suicide rate, and overall mortality for patients treated for bipolar disorder and schizophrenia.[39,40] This is important information, but it does not follow that mood stabilizing treatment or antipsychotic treatment is the culprit.

Other facets to consider are first that this study reflects the outcome of psychiatric and somatic treatment for transsexualism provided in Sweden during the 1970s and 1980s. Since then, treatment has evolved with improved sex reassignment surgery, refined hormonal treatment,[11,41] and more attention to psychosocial care that might have improved the outcome. Second, transsexualism is a rare condition and Sweden is a small country (9.2 million inhabitants in 2008). Hence, despite being based on a comparatively large national cohort and long-term follow-up, the statistical power was limited. Third, regarding psychiatric morbidity after sex reassignment, we assessed inpatient psychiatric care. Since most psychiatric care is provided in outpatient settings (for which no reliable data were available), underestimation of the *absolute* prevalences was inevitable. However, there is no reason to believe that this would change the *relative risks* for psychiatric morbidity unless sex-reassigned transsexual individuals were more likely than matched controls to be admitted to hospital for any given psychiatric condition.

Finally, to estimate start of follow-up, we prioritized using the date of a gender identity disorder diagnosis *after* changed sex status over *before* changed sex status, in order to avoid overestimating person-years at risk after sex-reassignment. This means that adverse outcomes might have been underestimated. However, given that the median time lag between the hospitalization before and after change of sex status was less than a year (see Methods), this maneuver is unlikely to have influenced the results significantly. Moreover, all deaths will be recorded regardless of this exercise and mortality hence correctly estimated.

Conclusion

This study found substantially higher rates of overall mortality, death from cardiovascular disease and suicide, suicide attempts, and psychiatric hospitalisations in sex-reassigned transsexual individuals compared to a healthy control population. This highlights that post surgical transsexuals are a risk group that need long-term psychiatric and somatic follow-up. Even though surgery and hormonal therapy alleviates gender dysphoria, it is apparently not sufficient to remedy the high rates of morbidity and mortality found among transsexual persons. Improved care for the transsexual group after the sex reassignment should therefore be considered.

Supporting Information

Table S1 Risk of various outcomes in sex-reassigned persons in Sweden compared to population controls matched for birth year and *birth sex*.
(DOCX)

Table S2 Risk of various outcomes in sex-reassigned persons in Sweden compared to controls matched for birth year and *final sex*.
(DOCX)

Author Contributions

Conceived and designed the experiments: CD PL AJ NL ML. Performed the experiments: MB AJ. Analyzed the data: CD PL MB AJ NL ML. Contributed reagents/materials/analysis tools: PL NL AJ. Wrote the paper: CD PL MB AJ NL ML.

References

1. World Health Organization (1993) The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic criteria for research. Geneva: WHO.
2. American Psychiatric Association, ed (1994) Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: APA.
3. Meyer W, Bockting W, Cohen-Kettenis P, Coleman E, DiCeglie D, et al. (2002) The Harry Benjamin International Gender Dysphoria Association's Standards of Care for Gender Identity Disorders, Sixth Version. Journal of Psychology & Human Sexuality 13: 1–30.
4. Cohen-Kettenis PT, Gooren LJG (1999) Transsexualism: A review of etiology, diagnosis and treatment. J Psychosom Res 46: 315–333.
5. Wålinder J, Thuwe I (1975) A social-psychiatric follow-up study of 24 sex-reassigned transsexuals. Göteborg, Sweden: Scandinavian University Books.
6. Eldh J, Berg A, Gustafsson M (1997) Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg 31: 39–45.
7. Johansson A, Sundbom E, Höjerback T, Bodlund O (2010) A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav 39: 1429–1437.
8. Sørensen T, Hertoft P (1982) Male and female transsexualism: the Danish experience with 37 patients. ArchSex Behav 11: 133–155.
9. De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, et al. (2005) Sexual and physical health after sex reassignment surgery. Arch Sex Behav 34: 679–690.
10. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ (1997) Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol Oxf 47: 337–342.

11. Gooren LJ, Giltay EJ, Bunck MC (2008) Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 93: 19–25.
12. Smith YL, van Goozen SH, Cohen-Kettenis PT (2001) Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. J Am Acad Child Adolesc Psychiatry 40: 472–481.
13. Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT (2005) Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med 35: 89–99.
14. Leavitt F, Berger JC, Hoeppner JA, Northrop G (1980) Presurgical adjustment in male transsexuals with and without hormonal treatment. J Nerv Ment Dis 168: 693–697.
15. Cohen Kettenis PT, van Goozen SH (1997) Sex reassignment of adolescent transsexuals: a follow-up study. J Am Acad Child Adolesc Psychiatry 36: 263–271.
16. Newfield E, Hart S, Dibble S, Kohler L (2006) Female-to-male transgender quality of life. Qual Life Res 15: 1447–1457.
17. Landén M, Wålinder J, Hambert G, Lundström B (1998) Factors predictive of regret in sex reassignment. Acta Psychiatrica Scandinavica 97: 284–289.
18. Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A (2005) Psychiatric comorbidity in gender identity disorder. J Psychosom Res 58: 259–261.
19. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, et al. (2010) Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf) 72: 214–231.
20. Landén M, Wålinder J, Lundström B (1996) Incidence and sex ratio of transsexualism in Sweden. Acta Psychiatrica Scandinavica 93: 261–263.
21. Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, et al. (2006) Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. Arch Sex Behav 35: 711–715.
22. Bodlund O, Kullgren G (1996) Transsexualism-General outcome and prognostic factors. A five year follow-up study of 19 transsexuals in the process of changing sex. Arch Sex Behav 25: 303–316.
23. Lindemalm G, Körlin D, Uddenberg N (1986) Long-term follow-up of "sex change" in 13 male-to-female transsexuals. Arch Sex Behav 15: 187–210.
24. Rauchfleisch U, Barth D, Battegay R (1998) [Results of long-term follow-up of transsexual patients]. Nervenarzt 69: 799–805.
25. Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller MD, et al. (2009) Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril 92: 1685–1689 e1683.
26. Zimmermann A, Zimmer R, Kovacs L, Einodshofer S, Herschbach P, et al. (2006) [Transsexuals' life satisfaction after gender transformation operations]. Chirurg 77: 432–438.
27. Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A (1999) The reported sex and surgery satisfactions of 28 postoperative male-to- female transsexual patients. Arch Sex Behav 28: 71–89.
28. Hepp U, Klaghofer R, Burkhard-Kubler R, Buddeberg C (2002) [Treatment follow-up of transsexual patients. A catamnestic study]. Nervenarzt 73: 283–288.
29. Lawrence AA (2003) Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Arch Sex Behav 32: 299–315.
30. Kaube H, Biemer E (1991) [Results of sex change operations in 30 transsexual patients: psychosocial and sexual adaptation–surgical complications]. Handchir Mikrochir Plast Chir 23: 276–278.
31. Dolmén L (2001) Brottsligheten i olika länder (Criminality in different countries). Stockholm: Brottsförebyggande rådet (the Swedish National Council for Crime Prevention).
32. Fazel S, Grann M (2006) The population impact of severe mental illness on violent crime. Am J Psychiatry 163: 1397–1403.
33. Landén M, Wålinder J, Lundström B (1998) Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. Acta Psychiatrica Scandinavica 97: 189–194.
34. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM (2010) Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clin Endocrinol (Oxf) 72: 1–10.
35. Landén M, Innala S (2000) Attitudes toward transsexualism in a Swedish national survey. Archives of Sexual Behavior 29: 375–388.
36. Mueller A, Gooren L (2008) Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 159: 197–202.
37. Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L (2009) Transsexualism in Serbia: a twenty-year follow-up study. J Sex Med 6: 1018–1023.
38. Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A (1999) The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. Arch Sex Behav 28: 71–89.
39. Ösby U, Brandt L, Correia N, Ekbom A, Sparén P (2001) Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 58: 844–850.
40. Tidemalm D, Langstrom N, Lichtenstein P, Runeson B (2008) Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. Bmj 337: a2205.
41. Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, et al. (2003) Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 88: 5723–5729.

Clinical Endocrinology (2010) **72**, 214–231 doi: 10.1111/j.1365-2265.2009.03625.x

ORIGINAL ARTICLE

Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes

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Summary

Objective To assess the prognosis of individuals with gender identity disorder (GID) receiving hormonal therapy as a part of sex reassignment in terms of quality of life and other self-reported psychosocial outcomes.

Methods We searched electronic databases, bibliography of included studies and expert files. All study designs were included with no language restrictions. Reviewers working independently and in pairs selected studies using predetermined inclusion and exclusion criteria, extracted outcome and quality data. We used a random-effects meta-analysis to pool proportions and estimate the 95% confidence intervals (CIs). We estimated the proportion of between-study heterogeneity not attributable to chance using the I^2 statistic.

Results We identified 28 eligible studies. These studies enrolled 1833 participants with GID (1093 male-to-female, 801 female-to-male) who underwent sex reassignment that included hormonal therapies. All the studies were observational and most lacked controls. Pooling across studies shows that after sex reassignment, 80% of individuals with GID reported significant improvement in gender dysphoria (95% CI = 68–89%; 8 studies; I^2 = 82%); 78% reported significant improvement in psychological symptoms (95% CI = 56–94%; 7 studies; I^2 = 86%); 80% reported significant improvement in quality of life (95% CI = 72–88%; 16 studies; I^2 = 78%); and 72% reported significant improvement in sexual function (95% CI = 60–81%; 15 studies; I^2 = 78%).

Conclusions Very low quality evidence suggests that sex reassignment that includes hormonal interventions in individuals with GID likely improves gender dysphoria, psychological functioning and comorbidities, sexual function and overall quality of life.

(Received 18 April 2009; returned for revision 4 May 2009; finally revised 6 May 2009; accepted 7 May 2009)

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Introduction

Therapy with cross-sex hormones is used as a primary sex reassignment intervention or as an adjunct to sex reassignment surgery in individuals with gender identity disorder (GID). Hormonal therapies clearly exert a rapid and direct effect on gender specific behaviours such as aggressiveness, arousal, verbal fluency and visuospatial abilities.[1] Several studies have reported sex reassignment to be associated with favourable changes in family, psychological and social life, sexual relationships and gender dysphoria, defined as the distress that originates from the difference between one's biological sex and one's basic sense of being a male or a female.[2–4]

Despite these putative benefits, individuals with GID who undergo this transition continue to have high prevalence of psychiatric comorbidities such as depression and anxiety disorders, as well as a suicide rate that is higher than that of the general population.[2,5] Hormonal therapies may also be associated with adverse effects that should be considered in addition to other costs and burdens of treatments. These adverse events have improved with the use of newer transdermal preparations and the routine administration of lower doses,[6,7] but may continue to be of concern to patients and providers.

We sought to systematically review the literature for the best available evidence regarding the benefits and risks of hormonal therapy administered in this context. In this manuscript, we summarize the available evidence about benefits in terms of self-reported outcomes such as the resolution of gender dysphoria and the effects on sexual function, psychiatric comorbidities and quality of life.

Methods

The report of this protocol-driven systematic review adheres to the standards for reporting Meta-analysis Of Observational Studies in Epidemiology (MOOSE).[8]

Eligibility criteria

We considered studies to be eligible for this review if they enrolled male-to-female (MF) or female-to-male (FM) individuals

Quality of life 15 years after sex reassignment surgery for transsexualism

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Objective: To evaluate quality of life and patients' satisfaction in transsexual patients (TS) after sex reassignment operation compared with healthy controls.
Design: A case–control study.
Setting: A tertiary referral center.
Patient(s): Patients after sex reassignment operation were compared with a similar group of healthy controls in respect to quality of life and general satisfaction.
Intervention(s): For quality of life we used the King's Health Questionnaire, which was distributed to the patients and to the control group. Visual analogue scale was used for the determination of satisfaction.
Main Outcome Measure(s): Main outcome measures were quality of life and satisfaction.
Result(s): Fifty-five transsexuals participated in this study. Fifty-two were male-to-female and 3 female-to-male. Quality of life as determined by the King's Health Questionnaire was significantly lower in general health, personal, physical and role limitations. Patients' satisfaction was significantly lower compared with controls. Emotions, sleep, and incontinence impact as well as symptom severity is similar to controls. Overall satisfaction was statistically significant lower in TS compared with controls.
Conclusion(s): Fifteen years after sex reassignment operation quality of life is lower in the domains general health, role limitation, physical limitation, and personal limitation. (Fertil Steril® 2009;92:1685–89. ©2009 by American Society for Reproductive Medicine.)

Key Words: Quality of life, transsexuals, patients' satisfaction, sex reassignment operation, long-term results

Based on legal applications for sex change (1981–1990), the estimated prevalence over 10 years in the former Federal Republic of Germany is 2.4:100,000 male-to-female (MTF) transsexuals (TS) and 1.0:100,000 female-to-male (FTM) TS (1, 2). In other European countries higher prevalences have been reported such as The Netherlands with 8.4:100,000 MTF and 3.3:100,000 FTM TS (3).

Sex reassignment surgery has been part of the treatment of transsexuality for >70 years and is widely accepted as therapeutic (4).

Individuals considering surgery and medical staff who serve as advisor and gatekeeper still have little reliable information concerning general outcome and quality of life after surgery. Groups such as the Harry Benjamin International Gender Dysphoria Association, which promotes Standards of Care for the provision of sex reassignment surgery (SRS), lack empirical and scientific information to assess the validity of their recommendations (5).

Little information is available on quality of life and factors associated with satisfaction or regret following sex reassignment surgery. Lawrence (6) found in a study of 232 MTF TS that dissatisfaction was most strongly associated with unsatisfactory functional results of surgery.

There is a growing consensus that subjective criteria may provide a more meaningful basis for evaluating sex reassignment surgery than the use of so-called objective criteria such as employment, choice of "appropriate" sexual partners or anatomic aspects assessed by the medical professionals (6).

The visual analogue scale (VAS) is a validated tool to assess health and satisfaction in patients, and is widely used for the investigation of pain and for measuring attitudinal attributes and quality of life (7).

The King's Health Questionnaire is a validated tool to assess quality of life, and is widely used tool to assess quality of life in incontinence and is validated in several languages including German (8). The questionnaire assesses the domains general health, role limitation, physical and personal limitation, emotions, sleep, incontinence, and symptom severity.

Received June 13, 2008; revised August 4, 2008; accepted August 27, 2008; published online November 6, 2008.
A.K. has nothing to disclose. C.B. has nothing to disclose. W.S. has nothing to disclose. P.K. has nothing to disclose. M.D.M. has nothing to disclose. M.B. has nothing to disclose.
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Sexologies 15 (2006) 126–133

available at www.sciencedirect.com

journal homepage: http://france.elsevier.com/direct/sexol

ORIGINAL ARTICLE / ARTICLE ORIGINAL

Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery

Suivi à long terme : résultats sur le plan psychosocial de la réassignation de sexe chez les transsexuels belges

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Available online 05 June 2006

KEYWORDS
Transsexual;
Gender identity disorder;
Sex reassignment surgery;
Outcome;
Psychosocial functioning, SCL-90;
Psychopathology

Abstract
Background. — To establish the benefit of sex reassignment surgery (SRS) for persons with a gender identity disorder, follow-up studies comprising large numbers of operated transsexuals are still needed.
Aims. — The authors wanted to assess how the transsexuals who had been treated by the Ghent multidisciplinary gender team since 1985, were functioning psychologically, socially and professionally after a longer period. They also explored some prognostic factors with a view to refining the procedure.
Method. — From 107 Dutch-speaking transsexuals who had undergone SRS between 1986 and 2001, 62 (35 male-to-females and 27 female-to-males) completed various questionnaires and were personally interviewed by researchers, who had not been involved in the subjects' initial assessment or treatment.
Results. — On the GAF (DSM-IV) scale the female-to-male transsexuals scored significantly higher than the male-to-females (85.2 versus 76.2). While no difference in psychological functioning (SCL-90) was observed between the study group and a normal population, subjects with a pre-existing psychopathology were found to have retained more psychological symptoms. The subjects proclaimed an overall positive change in their family and social life. None

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1158-1360/$ - see front matter
doi:10.1016/j.sexol.2006.04.002

Psychological Medicine, 2005, **35**, 89–99. © 2004 Cambridge University Press
DOI: 10.1017/S0033291704002776 Printed in the United Kingdom

Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals

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ABSTRACT

Background. We prospectively studied outcomes of sex reassignment, potential differences between subgroups of transsexuals, and predictors of treatment course and outcome.

Method. Altogether 325 consecutive adolescent and adult applicants for sex reassignment participated: 222 started hormone treatment, 103 did not; 188 completed and 34 dropped out of treatment. Only data of the 162 adults were used to evaluate treatment. Results between subgroups were compared to determine post-operative differences. Adults and adolescents were included to study predictors of treatment course and outcome. Results were statistically analysed with logistic regression and multiple linear regression analyses.

Results. After treatment the group was no longer gender dysphoric. The vast majority functioned quite well psychologically, socially and sexually. Two non-homosexual male-to-female transsexuals expressed regrets. Post-operatively, female-to-male and homosexual transsexuals functioned better in many respects than male-to-female and non-homosexual transsexuals. Eligibility for treatment was largely based upon gender dysphoria, psychological stability, and physical appearance. Male-to-female transsexuals with more psychopathology and cross-gender symptoms in childhood, yet less gender dysphoria at application, were more likely to drop out prematurely. Non-homosexual applicants with much psychopathology and body dissatisfaction reported the worst post-operative outcomes.

Conclusions. The results substantiate previous conclusions that sex reassignment is effective. Still, clinicians need to be alert for non-homosexual male-to-females with unfavourable psychological functioning and physical appearance and inconsistent gender dysphoria reports, as these are risk factors for dropping out and poor post-operative results. If they are considered eligible, they may require additional therapeutic guidance during or even *after* treatment.

INTRODUCTION

The phenomenon of transsexualism refers to individuals who are born with the normal sexual characteristics of one sex, but have the irrefutable conviction of belonging to the other.

Nowadays, many professionals who specialize in the treatment of transsexuals regard the conviction of transsexuals as belonging to someone of the other sex as authentic and, consequently, their wish for a sex change to be justified. The recommended procedure of the Harry Benjamin International Gender Dysphoria Association (Meyer *et al.* 2001), an international professional organization regarding transsexualism, is to approach the referral for sex reassignment (SR) in two phases. In the first phase, a DSM-IV diagnosis (APA, 1994) is made. In addition, the eligibility of the patient to move on to the second phase, the Real-life

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ECONOMIC IMPACT ASSESSMENT

GENDER NONDISCRIMINATION IN HEALTH INSURANCE

REGULATION FILE NUMBER: REG-2011-00023 **Dated April 13, 2012**

ACTUARIES: Ali Zaker-Shahrak, Lai Weng (Carol) Chio
ECONOMIST: Rani Isaac
HEALTH PROGRAM SPECIALIST: Jason Tescher

Description of Proposal

The proposed regulation clarifies the prohibition against discrimination on the basis of gender or sex. AB 1586 (2005) prohibits plans and insurers from denying an individual a plan contract or policy, or coverage for a benefit included in the contract or policy, based on the person's sex, defined as "includ[ing] a person's gender identity and gender related appearance and behavior whether or not stereotypically associated with a person's assigned sex at birth."

The proposed regulation specifies forms of gender discrimination that are a violation of the discrimination prohibition in California Insurance Code (Ins. Code) section 10140 including:

- Denying or cancelling an insurance policy on the basis of gender identity;
- Using gender identity as a basis for determining premium;
- Considering gender identity as a pre-existing condition; or
- Denying coverage or claims for health care services to transgender people when coverage is provided to non-transgender people for the same services.

The California Department of Insurance (the "Department") has determined that denying claims as listed in the bullet points above is a violation of the discrimination prohibition in Ins. Code section 10140. The proposed regulation clarifies the obligation of insurers to refrain from discriminatory practices and results in a prohibition on the denial of claims solely due to an individual's transgender status. Furthermore, the proposed is consistent with recently enacted legislation, AB 887 (Atkins, 2011), which specifically prohibited discrimination based on gender identity and gender expression. This document constitutes the Department's Economic Impact Assessment (EIA), which considers the economic impact of this prohibition and assesses whether and to what extent the proposed regulation affects the criteria set forth in Government Code Section 11346.3(b)(1).

Economic Impact Findings

The Department has determined that the adoption of the proposed regulation would have an insignificant and immaterial economic impact on the creation or elimination of jobs, the creation or elimination of new businesses, and the expansion of businesses in the State of California.

Prohibiting the four types of discrimination listed in the bullets above will be of significant benefit for transgender people and should thereby potentially improve their health and welfare since they have been targets of discrimination and violence.[1] The regulation may also have a positive impact on transgender worker safety. Since these workers will have improved access to health care coverage, under the proposed regulation, they should be in better health and more productive at work. However, while the proposed regulation may have a positive impact on the health, welfare and worker safety of the transgender population, which is a very small subset of California residents, the aggregate cost to the state population as a whole will be very insignificant (see "Prevalence of the Transgender Population" section).

The Department finds that nothing in the proposed regulation prohibits an insurer from using objective, valid, and up-to-date statistical and actuarial data or sound underwriting practices. While insurers may use someone's health status to determine their premium, analysis of the potential increase in claim costs from the proposed regulation shows that any such costs are immaterial and insignificant.

To arrive at these conclusions, Department staff conducted a thorough literature review, analyzed existing data, and obtained cost and premium data from employers. Department staff used a variety of data sources to reach these conclusions, including actuarial and utilization data related to potential increased claim costs resulting from the prohibition of the four types of discrimination listed in the bullets, above.

Impact on Employment and Business

Based on the very small size of the population that may be impacted by the proposed regulation, the Department has concluded that the proposed regulation will have an insignificant and immaterial impact on the creation or elimination of jobs, the creation of new business or the elimination of existing business, and the expansion of business currently doing business in California (see "Prevalence of the Transgender Population" section below).

Department staff have determined that the adoption of the proposed regulation will have an immaterial impact on extra demands for treatments, because of the low prevalence of the impacted population. Consequently, there will be immaterial changes in the labor force.

In addition, the proposed regulation requires equality of treatment. If a medically necessary treatment is not available to any insured, the insurer is not obligated to provide that treatment to transgender individuals. Because no new treatments are required, there is no impact on the creation or elimination of existing businesses, nor the expansion of established businesses in California.

Prevalence of the Transgender Population

Because the proposed regulation will give transgender Californians access to the same treatments offered to non-transgender Californians, the Department's analysis included a review of the number of the individuals in the California population that could contribute to increased claim

[1] See the "Impact on Health and Welfare" section.

costs. The transgender population is much smaller than the overall lesbian, gay, and bisexual population and is more difficult to track and follow due to the significant disenfranchisement and discrimination that transgender individuals face.[2] The Department has published a range of estimates (see table below).

The classic estimate for prevalence of transgender individuals (using gender identity disorder as a measurement) comes from the 1994 Diagnostic and Statistical Manual, Fourth Edition (DSM-IV), which reported 1:30,000 natal males and 1:100,000 natal females.[3] More recently, a 2009 review by Zucker and Lawrence concluded that the prevalence may be 3 to 8 times the numbers reported in the DSM-IV, based mostly on reports from Western European clinics.[4, 5]

In 2007, De Cuypere, et al., reviewed ten studies from eight countries; plus, they conducted their own study. "The prevalence figures reported in these ten studies range from 1:11,900 to 1:45,000 for male-to-female individuals and from 1:30,400 to 1:200,000 for female-to-male individuals. Some scholars have suggested that the prevalence is much higher, depending on the methodology used."[6]

Department staff utilized data from these studies, and estimates of the uninsured population, to arrive at a range of estimates for the insured transgender population in California based upon 2010 Census figures.[7]

Out of the 37.3 million California residents, transgender people make up between 0.0065 and 0.0173 percent of the total population in California, using the two highest estimates in order to be conservative (see the last two columns of the table below). When the rate of uninsured Californians (19 percent) is factored in, only 0.0052 to 0.014 percent of the state population would be impacted by the proposed regulation — or between 1,955 and 5,214 people. [8]

		Estimated Number of Transgender Individuals				
Total California Population	**Source**	**DSM-IV**	**De Cuypere - Low End**	**De Cuypere - High End**	**Zucker and Lawrence - 3 times DSM-IV**	**Zucker and Lawrence - 8 times DSM-IV**
18,517,830	Male	617	412	1,556	1,852	4,938
18,736,126	Female	187	94	616	562	1,499
37,253,956	Total	805	505	2,172	2,414	6,437
100%	Percentage of Total California Population	0.0022%	0.0014%	0.0058%	0.0065%	0.0173%
	Total Insured* (Total X .81)	652	409	1,760	1,955	5,214
	Percentage of Total California Population	0.0017%	0.0011%	0.0047%	0.0052%	0.0140%

[2] (Baker, Kesteren, Gooren, & Bezemer, 1993)
[3] (American Psychiatric Association, 1994)
[4] (Zucker & Lawrence, 2009)
[5] (Olson, Forbes, & Belzer, 2001)
[6] (The World Professional Association for Transgender Health, 2011)
[7] (U.S. Census Bureau, 2010)
[8] (The Kaiser Family Foundation, 2009)

Since the number of transgender people in the general population is so small, the subpopulation of insured individuals is even less significant. The following estimates by the Department of costs and utilization are conservative, considering that the transgender population has higher than average rates of poverty and unemployment and lower rates of insurance coverage. A 2008 survey conducted by the Transgender Law Center indicates that transgender people are twice as likely to live below the poverty line.[9] Because transgender people have less access to insurance coverage than average Californians, they are more likely to be covered by a public program and would not contribute to increased claims against private insurers.

Utilization and Impact on Claim Costs and Premiums

While there is limited actuarial data publically available on the impact that the Department's proposed regulation would have on claim costs and premiums, the Department has identified enough existing data to make conclusions about the economic impact of the regulation. Department staff reviewed data from five employers that have internal policies prohibiting discrimination in health care coverage and reviewed their related cost studies. For reasons discussed in the following section, the Department has concluded the impact on costs, due to the adoption of the proposed regulation, would be immaterial.

Utilization

Utilization data is important because it is used by insurers to calculate expected claim costs and then premiums. As utilization increases, the expected claim costs increase and in general the increase will be reflected in setting premiums. In this section, the Department presents data that indicates extremely low utilization resulting from elimination of gender discrimination, as would be expected with such a small population.

Once again, the proposed regulation requires that treatments available to non-transgender insureds not be denied based on an insureds actual or perceived gender identity or transgender status, as defined. If a medically necessary treatment is not available to any insured, the insurer is not obligated to provide that treatment to transgender individuals. Department staff used utilization data from employers that offer transgender employees equal health care benefits as a proxy for increased utilization that we may expect to see as a result of implementing the proposed regulations. Department staff determined that this data most closely represents the kind of increased utilization that we can expect based on prohibition of the four types of discrimination listed in the first section of this assessment.

While the move to eliminate this type of gender discrimination in health policies was rare among employers ten years ago, many more employers are adopting internal policies offering equal access to health care services for their transgender employees. The number of Fortune 500 companies that have eliminated discrimination in health care benefits offered to their transgender employees has increased from 49 in 2009 to 207 in 2012.[10] Presenters at the Out & Equal Workplace Summit 2011 indicated that the utilization, and thus costs, for prohibiting discrimination are very low. "[M]any employers around the country have eliminated the

[9] (Transgender Law Center, 2008)
[10] (Human Rights Campaign, 2012)

exclusions in their health plans…Utilization is very low and there has been little or no impact to premiums."[11]

Existing utilization data is limited due to extremely low utilization coupled with the concern that releasing this data could be traced back to individuals and violate health privacy laws. However, Department staff obtained and reviewed three sources of utilization data: (1) The City and County of San Francisco; (2) The University of California; and (3) Jamison Green and Associates report on utilization and costs to private companies with voluntary internal nondiscrimination policies similar to the proposed regulation.

The City and County of San Francisco (San Francisco) prohibited gender-based discrimination in 2001 for all City and County employees and their dependents. In the following five years, there were only 37 claims. A report by Jamison Green and Associates estimated that utilization rates (claimants per employee) ranged from 0.0325 to 0.104 claimants per thousand employees per year.[12]

In March 2012, the University of California (UC) released utilization and cost data from one of its health plan insurers, for the 6.5 years since UC first prohibited discrimination against transgender employees in its health care plans.[13] The utilization rates, as summarized in the table below, ranged from 0.011 to 0.093 claimants per thousand covered lives per year.[14] In order to make comparisons with other utilization data, the Department converted the UC data to utilization rates per 1,000 covered employees. Using a member-to-employee ratio of 2:1, Department staff arrived at utilization rates per 1,000 employees, from a minimum of 0.022 in CY 2006 to a maximum of 0.187 in CY 2009 (see far right column in table below).

Coverage Period	Number of Claimants	Average Covered Lives	Est. Average Number of Employees*	Utilization Rates per 1,000 covered lives	Utilization Rates per 1,000 employees*
Jul - Dec 2005	-	92,470	46,235	-	-
CY 2006	1	91,705	45,853	0.011	0.022
CY 2007	3	86,868	43,434	0.035	0.069
CY 2008	9	120,905	60,453	0.074	0.149
CY 2009	11	117,945	58,973	0.093	0.187
CY 2010	10	115,087	57,544	0.087	0.174
CY 2011	8	111,571	55,785	0.072	0.143
Total	42				
			Average utilization rates (excl. 2005 data)	0.062	0.124
			Min utilization rates (excl. 2005 data)	0.011	0.022
			Max utilization rates (excl. 2005 data)	0.093	0.187
*Estimated number of employees based on a member-to-employee ratio of 2:1					

[11] (Green, Wilson, & Fidas, 2011). Slide #5.
[12] (Wilson, 2012); Slide # 11
[13] (Manning, 2012)
[14] ibid.

Further underscoring evidence of extremely low utilization, the insurer reported that only 27 individuals sought treatments, some with multiple claims, over the period of 6.5 years.[15] Using the number of (distinct) members, rather than the number of distinct claims, Department staff obtained an average utilization rate of 0.039 per thousand covered lives per year. Department staff made the conversion because utilization data relying on covered lives is a more accurate representation of actual utilization. As expected, the average utilization rate per thousand covered lives (0.062 per thousand) is significantly lower than the utilization per thousand employees (0.124) because the rate per covered lives represents utilization spread across all insureds.

In addition, a report issued by Jamison Green and Associates estimated utilization rates in the range of 0.0015 to 0.325 per thousand employees per year, based on interviews with fifteen Fortune 500 companies who have eliminated the discriminatory policies.[16] Their broader estimates discussed below included the experience of San Francisco.

The table below summarizes the utilization rates from all three sources mentioned above.

	Utilization Rates per 1,000 employees per year		
Case	City and County of San Francisco	University of California	Sample of Private Employers
Minimum	0.0325	0.022	0.0015
Maximum	0.104	0.187	0.325

The utilization rates for San Francisco and UC fall within the range of utilization estimates of Jamison Green and Associates discussed above.

Claim Costs and Premium History

The Department augmented the limited claim cost and utilization data available by reviewing premium data from several employers to determine the additional amount their insurers have been charging to extend equal coverage to transgender employees and dependents.

For San Francisco, the initial cost per employee was $1.70 per member per month (PMPM) in 2001. Due to low utilization, San Francisco reduced the PMPM to $1.16 in 2004-2005 and the city's self-insured plan reduced its charge to $0.50 PMPM. As of July 1, 2006, the cost data demonstrated that no separate rate was required, so the charge was removed entirely. Initial claims were first subject to a lifetime maximum of $50,000 then increased to $75,000 in 2004.[17]

[15] There were 27 unduplicated individuals who received treatment during this time period. There were 42 claimants because some procedures for the same individual occurred over more than one year.

[16] (Wilson, 2012) Slide #13

[17] (The City and County of San Francisco Human Rights Commission, 2007)

The University of California eliminated transgender discrimination in 2005 without being charged an additional premium.[18] Claim cost data from the UC health plan with the largest enrollment shows that the claim costs PMPM attributed to the elimination were very low. The maximum of claim costs during the 6.5 years was $0.20 PMPM, or 0.05 percent of the total premium.

As of January 1, 2012, the City of Berkeley removed discriminatory provisions within its health plans. Berkeley's insurers charged a premium of 0.2 percent of the total annual budget for healthcare benefits. The total projected monthly increase was 0.25 percent (223 covered lives in one plan) and 0.19 percent (938 covered lives in another plan) as of March 2012.[19]

Two other cities have had experiences similar to Berkeley's. The City of Portland removed discriminatory policies beginning July 1, 2011. The cost projection for Portland was $32,302 out of a total $41,615,000 health care budget – a 0.08 percent increase.[20] The City of Seattle absorbed a premium increase of $200,000 per year of a total $105 million health care budget – just 0.19 percent of total health costs based on insurer estimates of increased utilization.[21]

It is a standard practice for insurers to charge a premium to cover expected claim costs of the proposed regulation, administrative expenses, taxes, profit and any provisions for adverse deviation. When credible cost and utilization data is absent or limited for new benefits, insurers tend to be conservative by including a larger provision for adverse deviation. This is evidenced by San Francisco's experience, where "[f]rom July 2001 through July 2006, the grand total of reported monies collected (for this purpose) is $5.6 million. The grand total of reported monies expended is $386,417."[22] Since cost assumptions were nearly 15 times higher than actual claims, the city eventually eliminated the additional premium.

Using the impact on premiums as a proxy for anticipated increased claim costs, the range of the impact on costs for the proposed regulation would be a minimum of no increase (the case of San Francisco and the University of California), to a maximum increase of 0.2 percent in expected claim costs (the cases of Berkeley and Seattle). However, changes to policies in Berkeley and Seattle were recent, limiting data availability. As stated before, the 0.2 percent estimate may very likely include a large provision for adverse deviation. The Department's conclusion is supported by the actual claims data collected for the UC system, which shows the claims costs accounted for only 0.05 percent of premiums.

In addition to the employer information, Department staff also reviewed the Sylvia Rivera Law Project white paper discussing the impact of a similar prohibition for Medicaid in the State of New York. "A preliminary estimate by the New York State Department of Health in 2010 approximated that it would cost about $1.7 million to cover gender-confirming care through

[18] (Manning, 2012)
[19] (Hodgkins, 2012)
[20] (The City of Portland, Oregon, 2011)
[21] (Freiboth, 2012)
[22] (The City and County of San Francisco Human Rights Commission, 2007)

Medicaid. As the state Medicaid budget totals $52 billion, this represents only 0.003 percent of the total budget."[23]

Based on evidence of low utilization and prevalence rates shown above, the Department has determined that the impact on costs or increases in premiums due to the adoption of the proposed regulation would be immaterial.

Utilization Assumptions

There are a number of assumptions that contribute to lower-than-expected utilization seen in San Francisco. Like any other condition, treatment options for GID vary greatly and not all transgender people with the diagnosis will undergo surgical intervention. It appears that utilization projections are made with:

> …the belief that all transgender people undergo genital surgery as the primary medical treatment for changing gender. In fact, gender-confirming healthcare is an individualized treatment that differs according to the needs and pre-existing conditions of individual transgender people. Some transgender people undergo no medical care related to their expression of a gender identity that differs from their birth-assigned sex. Others undergo only hormone therapy treatment or any number of surgical procedures.[24]

The assumption that treatment utilization and costs are the same for each transgender person is reflected in the significant difference between premium charges by insurers and actual utilization costs and evidenced in the wide range of claims costs reported by the University of California. The claims varied from $67 to $86,800 with an average cost of $29,929 per transgender person requiring treatment.

Additional factors that impact utilization and cost include, but are not limited to:

- Transgender insureds may have already undergone treatment;
- Surgical treatment for gender identity disorder (GID) is usually a once-in-a-lifetime event, and many costs are spread over a lifetime, and do not occur in just a single year;
- Transgender people do not always have a diagnosis of GID and thus have no medically necessary indication for treatment;
- Almost all surgical treatments for treatment of GID are treatments that are provided to non-transgender insureds for other indications; and
- Other health factors can contraindicate treatment.

[23] (The Sylvia Rivera Law Project, 2011)
[24] (Spade, 2010)

A detailed analysis of the impact of each of these assumptions on utilization is beyond the scope of this assessment, but is illustrative of what may be the reasons for the apparent gap between premiums charged to employers for prohibiting health care discrimination against transgender insureds and the actual reported utilization and cost.

In addition, the Department believes that there may be a possible spike in demand for such services in the first few years after the adoption of the proposed regulation due to the possible existence of some current unmet demand. This may lead to higher costs, in the near-term, following the adoption of the proposed regulation. While this is possible, this was not the experience of the University of California or San Francisco. In any case, the small size of the impacted population will likely make the magnitude of such an increase insignificant and immaterial.

Impact on Health and Welfare

As discussed in the *Prevalence* and the *Utilization and Claims* sections, prohibiting the four types of discrimination listed in the bullets on page one will be of significant benefit for a very small class of California residents who are directly impacted. The proposed regulation should thereby potentially improve their health and welfare since transgender people have been targets of discrimination and violence.[25] The proposed regulation may also improve worker safety, as explained above. However, while the Department found that the proposed regulation may have a significant beneficial impact on the health, welfare and safety of the transgender population, the aggregate costs will be very insignificant. The Department has determined that the benefits of eliminating discrimination far exceed the insignificant costs associated with implementation of the proposed regulation. Based on this assessment, the Department has determined that there are no significant adverse impacts of the regulation to the health and welfare of California residents, nor will it impact overall worker safety, and the state's environment.

Further, the Department's evidence suggests that benefits will accrue to insurance carriers and employers as costs decline for the treatment of complications arising from denial of coverage for treatments. The evidence suggests that there may be potential cost savings resulting from the adoption of the proposed regulation in the medium to long term, such as lower costs associated with the high cost of suicide and attempts at suicide, overall improvements in mental health and lower rates of substance abuse, as discussed in the following section.

The Benefit and Cost Savings of Suicide Reduction[26]

One of the most severe results of denying coverage of treatments to transgender insureds that are available to non-transgender insureds is suicidal ideation and attempts. The Centers for Disease Control and Prevention estimate the average acute medical costs of a single suicide completion or attempt in the United States is $2,596 and $7,234 respectively.[27] This only includes acute care and hospitalization costs. While there are studies that provide higher estimated costs per suicide attempt and completion, we choose to conservatively use the lower bound cost to keep estimates

[25] (Tannis, Grant, & Mottat, 2010)
[26] (Gorton, 2011)
[27] (The Centers for Disease Control, 2010)

as relevant to health insurers as possible. [28,29] A more in-depth analysis might include the costs of mental health treatment or other medical costs following a suicide attempt.

A meta-analysis published in 2010 by Murad, et al., of patients who received currently excluded treatments demonstrated that there was a significant decrease in suicidality post-treatment. The average reduction was from 30 percent pretreatment to 8 percent post treatment.[30]

De Cuypere, et al., reported that the rate of suicide attempts dropped dramatically from 29.3 percent to 5.1 percent after receiving medical and surgical treatment among Dutch patients treated from 1986-2001.[31]

According to Dr. Ryan Gorton, "In a cross-sectional study of 141 transgender patients, Kuiper and Cohen-Kittenis found that after medical intervention and treatments, suicide fell from 19 percent to zero percent in transgender men and from 24 percent to 6 percent in transgender women.[32])"[33]

Clements-Nolle, et al., studied the predictors of suicide among over 500 transgender men and women in a sample from San Francisco and found a prevalence of suicide attempts of 32 percent.[34] In this study, the strongest predictor associated with the risk of suicide was gender based discrimination which included "problems getting health or medical services due to their gender identity or presentation."[35] According to Gorton, "Notably, this gender-based discrimination was a more reliable predictor of suicide than depression, history of alcohol/drug abuse treatment, physical victimization, or sexual assault."[36]

A recent systematic review of largely American samples gives a suicide attempt rate of approximately one in every three individuals with higher rates found among adolescents and young adults.[37] According to Dr. R. Nicholas Gorton, MD, who treats transgender people at a San Francisco Health Clinic, "The same review also noted that while mental health problems predispose to suicidality, a significant proportion of the drivers of suicide in the LGBT population as a whole is minority stress." He continues to conclude that, "[f]or transgender people such stress is tremendous especially if they are unable to 'pass' in society. Surgical and hormonal treatments — that are [also] covered for non-transgender insureds — are specifically aimed at correcting the body so that it more closely resembles that of the target gender, so providing care significantly improves patients' ability to pass and thus lessens minority stress."[38]

These studies provide overwhelming evidence that removing discriminatory barriers to treatment results in significantly lower suicide rates. These lower rates, taken together with the estimated

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[28] (Yang & D.Lester, 2007)
[29] (Corso P, 2007)
[30] (Murad M, 2010)
[31] (DeCuypere, 2006)
[32] (Kuiper M, 1988)
[33] (Gorton, 2011)
[34] (Clements-Nolle K, 2006)
[35] (Clements-Nolle, Marx, & and Katz, 2006)
[36] (Gorton, 2011)
[37] (Haas, 2011)
[38] (Gorton, 2011)

costs of a suicide attempt and completion, demonstrate that the proposed regulation will not only save insurers from the costs associated with suicide, but prevent significant numbers of transgender insureds from losing their lives.

Additional Benefits

Overall improvements in mental health. Transgender insureds who have access to treatment see rates of depression drop and anxiety decrease. Evidence supporting this conclusion comes from a meta-analysis of 28 studies showing that 78 percent of transgender people had improved psychological functioning after treatment.[39] In another recent study, transgender women who had had any relevant surgeries had mental health scores comparable to women in general, while those who were not able to access care scored much lower on mental health measures.[40] In another study, participants improved on 13 out of 14 mental health measures after receiving treatments.[41] This overall improvement in mental health and reduction in utilization of mental health services could be a source of cost savings for employers, insurers, and insureds.

Substance abuse rates decline. There are numerous studies that provide evidence that substance abuse rates decline including one where participants, "describe how substance use was a coping mechanism for their gender dysphoria before they had access to treatment."[42, 43] Another study found an overall reduction in substance use after receiving treatment.[44]

Further, the Sylvia Rivera Law Project suggests that treatment for GID could combat other types of substance abuse since it is well known that "[i]ncreased smoking and drug and alcohol use correlates with increased rates of lung cancer, heart disease, stroke, and liver disease."[45]

HIV Rates and Care. Transgender people have significantly higher rates of HIV than the general population (28 percent in a meta-analysis[46] as compared to a general population rate of 0.6 percent).[47] It is also significant that studies show "high rates of adherence to HIV care for trans people when combined with hormonal treatment."[48, 49] This is particularly relevant to insurers because it provides evidence that offering treatment may reduce the long-term costs of treatment for HIV/AIDS. It is particularly relevant for the welfare of all Californians because, "[w]hen compliant with care, HIV-positive people stay healthier longer and are far less likely to transmit the virus to others."[50]

Other Benefits. Transgender people who are denied access to treatment and suffer from dysphoria associated with gender identity disorder sometimes turn to self-medication for relief.

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[39] (Murad M, 2010)
[40] (Ainsworth & Spiegel, 2010).
[41] (Smith Y, 2005)
[42] (The Sylvia Rivera Law Project, 2011)
[43] (Cole, 1997)
[44] (Rehman, 1999)
[45] (The Sylvia Rivera Law Project, 2011)
[46] (Operario D., 2010)
[47] (United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2007)
[48] (The Sylvia Rivera Law Project, 2011)
[49] Grimaldi J; Jacobs J. (1998.) "The HIV/Hormone Bridge, *Int Conf AIDS; 12*: 981, abstract no. 571/44225.
[50] (The Sylvia Rivera Law Project, 2011)

Silicone injections, for example, are sometimes used in lieu of medically available treatments. Prevalence of this has been documented in needs assessments in Washington D.C., Chicago, and Los Angeles, where respondents reported having injected silicone into their bodies at a rate of 25, 30, and 33 percent of the time, respectively.[51, 52, 53] Construction-grade silicone is used to alter body shape sometimes resulting in deadly consequences.[54] Several researchers suggest that lack of early access to GID treatments and care costs more.

Increased socioeconomic status for transgender insureds. Lack of access to treatment due to coverage denials also results in a greater likelihood of adverse socioeconomic consequences for the insured. A single group pre- and post-study demonstrated improvements in socioeconomic status or employment status in transgender patients after hormonal and surgical treatment.[55] Additional studies conclude that transgender persons have higher employment rates after they have access to treatments.[56]

For the reasons cited above, Department staff concluded that ending these four types of discrimination will cost little or nothing in the short run and may produce longer-term cost savings and improved health benefits for transgender people.

[51] (Xavier, 2000)
[52] (Bostwick, 2001)
[53] (Reback, Simon, Bemis, & Gatson, 2001)
[54] (Komenaka, 2004); (Fox, 2004); (Hage, 2001).
[55] (Bodlund O, 1996)
[56] (Grant, 2010); (Murad M, 2010); (Rakic, 1996).

Works Cited

Ainsworth, T., & Spiegel, J. (2010). Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Quality of Life Research, 19*, 1019–1024.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.* Washington, D.C.: American Psychiatric Association.

Baker, A., Kesteren, P. V., Gooren, L., & Bezemer, P. (1993). The prevelence of transexualism in the Netherlands. *Acta Phsychiatrica Scandinavica*(87), 237-238.

Bodlund, O., & Gunnar, K. (1996). Transsexualism – General outcome and prognostic factors: A 5 year follow-up study of 19 TSs in the process of changing sex. *Arch. Sexual Behavior, 25*, 303-316.

Bostwick, W., & Kenagy, G. (2001). *Health and social service needs of transgendered people in Chicago.* Chicago: Jane Addams College of Social Work, University of Illinois at Chicago.

Census Bureau. (2010). *Profile of General Demographic Characteristics, California*. Retrieved from Table DP-1: www.census.gov

Centers for Disease Control. (2010). *Fact Sheet: The Medical Cost Associated with Suicide in the United States*. Retrieved 2012, from http://www.cdc.gov/ncipc/factsheets/images/Medical_Costs.pdf;

City and County of San Francisco Human Rights Commission, The. (2007). *Report on San Francisco City and County Transgender Health Benefit.* San Francisco: The City and County of San Francisco.

City of Portland, Oregon. (2011). *Mayor Sam Adams*. Retrieved from http://www.portlandonline.com/mayor/?a=351892&c=49278

Clements-Nolle, K., Marx, R., & and Katz, M. (2006). Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *Journal of Homosexuality, 53*(3), 53-69.

Cole, C., O'Boyle, M., Emory, L., & Meyer, W. (1997). Co-morbidity of Gender Dysphoria and Other Major Psychiatric Diagnoses. *Archives of Sexual Behavior, 26*(1), 13-19.

Corso, P., Mercy, J., Simon, T., Finkelstein, E., & Miller, T. (2007). Medical Costs and Productivity Losses Due to Interpersonal and Self-Directed Violence in the United States 32(6) : 474-482. *Am J Prev Med, 32*(6), 474-482.

De Cuypere, G. E. (2006). Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *Sexologies, 15*, 126–133.

Fox, L., Geyer, A., Husain, S., Della-Latta, P., & Grossman, M. (2004). Mycobacterium abscessus cellulitis and multifocal abscesses of the breasts in A transsexual from illicit intramammary injections of silicone. *Journal of the American Academy of Dermatology, 50*, 450.

Freiboth, R. (2012, March 6). Transgender Benefit Insurance Premium Increase Data. (email communication). (C. o. Manager, Ed.) Seattle, WA.

Gorton, R. N. (2011). *The Costs and Benefits of Access to Treatment for Transgender People.* Prepared for the San Francisco Department of Public Health, San Francisco.

Green, J., Wilson, A., & Fidas, D. (2011). *Transgender Inclusive Health Benefits: Costs, Medical Models & Best practices.* Dallas.

Haas, A., Eliason, M., Mays, V., Mathy, R., Cochran, S., D'Augelli, A., . . . Diamond, G. (2011). Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: Review and recommendations. *Journal of Homosexuality, 58*(1), 10-51.

Hage, J. (2001). The devastating Outcome of Massive Subcutaneous Injection of Highly Viscous Fluids In Male to Female Transsexuals. *Plastic and Reconstructive Surgery*, 734.

Hodgkins, D. (2012, March 15). Transgender Benefit Insurance Premium Increase Data. (email communication). Berkeley, CA: City of Berkeley, Department of Human Resources.

Human Rights Campaign. (2012). *Corporate Equality Index 2012.* Washington, D.C.: Human Rights Campaign.

Institute of Medicine of the National Academies. (2011). *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding.* National Academies, Board on the Health of Select Populations. Washington, D.C.: The National Academies Press.

Kaiser Family Foundation, The. (2009). *State Health Facts*. Retrieved 2011, from http://www.statehealthfacts.org/profileglance.jsp?rgn=6

Komenaka, I. (2004). Free silicone injection causing polyarthropathy and septic shock. *The Breast Journal, 10*(2), 160.

Kuiper, M., & Cohen-Kittenis, P. (1988). Sex reassignment surgery: A study of 141 Dutch transsexuals. *Arch Sex Behav, 5*, 439-457.

Manning, J. (2012, April). University of California Transgender Benefit Cost and Utilization Letter. *University of California Transgender Benefit Review 2012*(email communication). Oakland, CA, United States: University of California, Office of the President.

Murad, M., Elamin, M., Garcia, M., Mullan, R., Murad, A., Erwin, P., & Montori, V. (2010). Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clinical Endocrinology, 72*, 214-231.

Olson, J., Forbes, C., & Belzer, M. (2001, February). Management of the Transgender Adolescent. *Archives of Pediatrics and Adolescent Medicine, 165*(2), 171-176. Retrieved from http://archpedi.ama-assn.org/cgi/content/full/165/2/171

Operario, D., & Nemoto, T. (2010). HIV in Transgender Communities: Syndemic Dynamics and a Need for Multicomponent Interventions. *Journal of Acquired Immune Deficiency Syndrome, 55*(2), S91–S93.

Rakic, Z., Starcevic, V., Maric, J., & Kelin, K. (1996). The Outcome of Sex Reassignment Surgery in Belgrade: 32 Patients of Both Sexes. *Archives of Sexual Behavior, 25*, 515.

Reback, C., Simon, P., Bemis, K., & Gatson, B. (2001). *Los Angeles Transgender Health Study: Community Report.* Los Angeles.

Rehman, J., Lazar, S., Benet, A., Schaefer, L., & Melman, A. (1999). The Reported Sex and Surgery Satisfactions of 28 Postoperative Male to-Female Transsexual Patients. *Archives of Sexual Behavior*, 71.

Smith, Y., Van Goozen, S., Kuiper, A., & Cohen-Kettenis, P. (2005). Sex Reassignment: Outcomes and Predictors of Treatment for Adult and Adolescent Transsexuals. *Psychological Medicine*, 35, 89-99.

Spade, D., Arkles, G., Duran, P., Gehi, P., & Nguyen, H. (2010). Medicaid Policy & Gender-Confirming Helathcare for Trans Prople: An Interview with Advocates. *Seattle Journal for Social Justice, 8*(2), 497-514.

Sylvia Rivera Law Project, The. (2011). *Eliminating the Medicaid Exclusion for Transition-Related Care in NYS: Good Public Health, the Right Thing to Do and Ultimately a Cost-Saving Measure.* New York: Sylvia Rivera Law Project.

Tannis, J., Grant, J., & Mottat, L. (2010). *Injustice at Every Turn: A Report of the National Transgender Discrimination Survey.* Washington, D.C.: National Center for Transgender Equality and National Gay and Lesbian Task Force.

Transgender Law Center. (2008). *The State of Transgender California: A report on the 2008 California Transgender Economic Health Survey.* San Francisco: The Transgender Law Center.

United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). (2007). *AIDS Epidemic Update*. Retrieved from http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.

Wilson, A. (2012). *Transgender-Inclusive Health Benefits: Costs, Data for Cost Calculation.* Jamison Green and Associates.

World Professional Association for Transgender Health, The. (2011). *Standards of Care for the Health of Transexual, Transgender, and Gender Nonconforming People, 7th ed.* The World Professional Association for Transgender Health.

Xavier, J. (2000). *The Washington Transgender Needs Assessment Survey.* Washington, D.C.: The Administration for HIV and AIDS of the District of Columbia Government.

Yang, B., & Lester, D. (2007). Recalculating the Economic Cost of Suicide. *Death Studies, 31*, 351–361.

Zucker, K., & Lawrence, A. (2009). Epidemiology of Gender Identity Disorder. *International Journal of Transgenderism, 11*(1), 8-18.

WPATH WORLD PROFESSIONAL ASSOCIATION for TRANSGENDER HEALTH

Standards of Care

for the Health of Transsexual, Transgender, and Gender-Nonconforming People

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7th Version[1] | www.wpath.org

ISBN: X-XXX-XXXXX-XX

1 This is the seventh version of the *Standards of Care* since the original 1979 document. Previous revisions were in 1980, 1981, 1990, 1998, and 2001. Version seven was published in the International Journal of Transgenderism, 13(4), 165–232. doi:10.1080/15532739.2011.700873

Purpose and Use of the *Standards of Care*

The World Professional Association for Transgender Health (WPATH)[I] is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health. The vision of WPATH is a world wherein transsexual, transgender, and gender-nonconforming people benefit from access to evidence-based health care, social services, justice, and equality.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the articulation of *Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People*. The *SOC* are based on the best available science and expert professional consensus.[II] Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the *SOC* to other parts of the world are necessary. Suggestions for ways of thinking about cultural relativity and cultural competence are included in this version of the *SOC*.

The overall goal of the *SOC* is to provide clinical guidance for health professionals to assist transsexual, transgender, and gender-nonconforming people with safe and effective pathways to achieving lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment. This assistance may include primary care, gynecologic and urologic care, reproductive options, voice and communication therapy, mental health services (e.g., assessment, counseling, psychotherapy), and hormonal and surgical treatments. While this is primarily a document for health professionals, the *SOC* may also be used by individuals, their families, and social institutions to understand how they can assist with promoting optimal health for members of this diverse population.

WPATH recognizes that health is dependent upon not only good clinical care but also social and political climates that provide and ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that promote tolerance and equity

I Formerly the Harry Benjamin International Gender Dysphoria Association

II The *Standards of Care (SOC), Version 7,* represents a significant departure from previous versions. Changes in this version are based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender-nonconforming people beyond hormone therapy and surgery (Coleman, 2009a, b, c, d).

Section 4.0

Guidelines

Bariatric Surgery Guideline

Question: should the current bariatric surgery guideline be clarified?

Question source: Lyle Jackson, OHP Medical Director; DMAP

Issues:

1) Several issues have been raised about details in the bariatric surgery guideline which need clarification/updating.

From DMAP:

- Footnote 4 is not connected to anything in the main body of text and it refers to criteria #1, #2, and #3 when it should refer to A), B), and C).
- Footnote 2 says the center must be certified by the American College of Surgeons (ACS) or the American Society for Metabolic and Bariatric Surgery (ASMBS). These two certifications are now combined. The certification is now by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP).
- Also, this may not matter but, Medicare is no longer requiring bariatric surgeries be done at certified centers. This went into effect 9/24/13.

:

2) There is some confusion about when bariatric surgery is covered on line 33 (diabetes) and when covered on line 616 (obesity).

From Dr. Jackson:

There is so much confusion in the interpretation of this guideline by the providers' staff, that every year we are constantly educating new staff members. The problem with Guideline 8 is that it combines two lines (30 and 594) together, one of which is covered and the other is non covered. The wording is very confusing. The solution is so easy. Just separate them by putting them in two separate guidelines as you did for Guidelines 37 and Guideline 57.

If you cannot separate GN8 into separate guidelines, is it possible to separate the two sentences starting with " B) For inclusion on Line …" by either separating them by putting them in separate paragraphs with a space between them or by separating them by using B) 1) For inclusion on Line 33…and B) 2) For inclusion in Line 616… ?

The sentence starting with "For inclusion on Line 616..." is very awkward and confusing. I would rewrite that sentence by the following: For inclusion on Line 616: a) the member must have a BMI>=35 with at least one significant co-morbid condition not including DMll, such as OSA and high blood pressure or b) the member must have a BMI>=40 with no significant morbidity including DMll.

Current Guideline Note

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,594

Bariatric surgery for obesity is included on Line 30 TYPE II DIABETES MELLITUS, and Line 594 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE) under the following criteria:

A) Age ≥ 18
B) For inclusion on Line 30: BMI ≥ 35 with co-morbid type II diabetes. For inclusion on Line 594: BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity.
C) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.
D) Participate in the following four evaluations and meet criteria as described.
    1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
        a) Evaluation to assess potential compliance with post-operative requirements.
        b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.
        c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
        d) Patient with previous psychiatric illness must be stable for at least 6 months.
    2) Medical evaluation: (Conducted by OHP primary care provider)
        a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
        b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
        c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
    3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
        a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
        b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure[3] and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
    4) Dietician evaluation: (Conducted by licensed dietician)

a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
b) Counseling in dietary lifestyle changes

E) Participate in additional evaluations:
1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

[1] Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

[2] All surgical services must be provided by a program with current certification by the American College of Surgeons (ACS) or the American Society for Metabolic and Bariatric Surgery (ASMBS), or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365;appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of surgical outcomes. If the program is still pursuing ACS or ASMBS certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).

[3] Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.

[4] The patient must meet criteria #1, #2, and #3, and be referred by the OHP primary care provider as a medically appropriate candidate, to be approved for evaluation at a qualified bariatric surgery program.

HERC staff recommendation:

1) Change GN 8 to read as below
2) Consider removing requirement for surgery to be performed at a Center of Excellence to align with current CMS rules

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,594

Bariatric surgery ~~for obesity~~ is included ~~on Line 30 TYPE II DIABETES MELLITUS, and Line 594 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE)~~ under the following criteria:

A) Age ≥ 18

B. The patient has

1) a BMI ≥ 35 with co-morbid type II diabetes for inclusion on Line 30 TYPE II DIABETES MELLITUS; OR

2) BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity for inclusion on Line 594 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE)

~~For inclusion on Line 30: BMI ≥ 35 with co-morbid type II diabetes. For inclusion on Line 594: BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity.~~

C) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.

D) Participate in the following four evaluations and meet criteria as described.

1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
   a) Evaluation to assess potential compliance with post-operative requirements.
   b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.
   c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
   d) Patient with previous psychiatric illness must be stable for at least 6 months.
2) Medical evaluation: (Conducted by OHP primary care provider)
   a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
   b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.

c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.

3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
   a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
   b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure[3] and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
4) Dietician evaluation: (Conducted by licensed dietician)
   a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
   b) Counseling in dietary lifestyle changes

E) Participate in additional evaluations:
1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

[1] Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

[2] All surgical services must be provided by a program with current certification by the ~~American College of Surgeons (ACS) or the American Society for Metabolic and Bariatric Surgery (ASMBS),~~ Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365;appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of surgical outcomes. If the program is still pursuing MBSAQIP ~~ACS or ASMBS~~ certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).

[3] Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.

[4] ~~The patient must meet criteria #1, #2, and #3, and be referred by the OHP primary care provider as a medically appropriate candidate, to be approved for evaluation at a qualified bariatric surgery program~~.

Rehabilitation Guideline Clarifications

Issue: The Rehabilitation Guideline was extensively edited at the May, 2014 VBBS meeting. HERC staff has noted two clarifications to the accepted wording which would improve the guideline.

Recommendation:

1) Adopt the slightly modified Rehabilitation Guideline as shown below

GUIDELINE NOTE 6, REHABILITATIVE THERAPIES

Lines 37,50-52,64,74-76,78,80,85,89,90,94,95,98-101,108,109,115,116,122,129,139,141-143,145,146,158,161,167,179,184,185,189,190,192,194,195,201,202,208,209,216,226,237,239,270,271,273,274,279,288,289,293,297,302,304,307-309,318,336,342,349,350,363,367,369,375,376,378,382,384,385,387,400,406,407,434,441,443,448,455,467,478,489,493,507,516,535,549,562,580,597,619,638

Physical, occupational and speech therapy, and cardiac and vascular rehabilitation are only included on these lines when the following criteria are met:

1) therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide the ~~physical, occupational, or speech~~ therapy,
2) there is objective, measurable documentation of progress toward the therapy plan of care goals and objectives,
3) the therapy plan of care requires the skills of a ~~therapist~~ medical provider, and
4) the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

Lymphedema for June 2014

Issues: The current lymphedema guideline needs three modifications due to recent VBBS decisions:

1) A new lymphedema line was created at the May, 2014 VBBS meeting which combined all lymphedema diagnoses which currently are on 3 separate lines. The current lymphedema guideline needs to be modified to reflect this line change for the next biennial review List.

2) At the May, 2014 meeting, the VBBS modified the rehabilitation guideline to remove visit number restrictions. The lymphedema guideline refers to these visit restrictions, and needs this portion removed beginning with the October 1, 2014 Prioritized List.

3) At the May, 2014 meeting, sub-committee members expressed interest in making very clear their intent to cover treatments for lymphedema, including compression stockings, even when no ulcer or other complication was present. Experts suggested putting this coverage intent into the lymphedema guideline.

HERC staff recommendations:

1) Modify the lymphedema guideline as shown below (#1) for the October 1 List until the next biennial review List
2) Modify the lymphedema guideline as shown below (#2) beginning with the next biennial review List

#1 (October 1, 2014 Prioritized List)
GUIDELINE NOTE 43, LYMPHEDEMA

Lines 427,577,579

Lymphedema treatments are included on these lines when medically appropriate. These services are to be provided by a licensed practitioner who is certified by one of the accepted lymphedema training certifying organizations or a graduate of one of the National Lymphedema Network accepted training courses within the past two years. The only accepted certifying organization at this time is LANA (Lymphology Association of North America; http://www.clt-lana.org). ~~Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE THERAPIES.~~ It is the intent of the HERC that compression dressings and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

#2 (Biennial review List)
GUIDELINE NOTE 43, LYMPHEDEMA

Line~~s 427,577,579~~ XXX (new lymphedema line)

Lymphedema treatments are included on this line ~~these lines~~ when medically appropriate. These services are to be provided by a licensed practitioner who is certified by one of the accepted lymphedema training certifying organizations or a graduate of one of the National Lymphedema Network accepted training courses within the past two years. The only accepted certifying organization at this time is LANA (Lymphology Association of North America; http://www.clt-lana.org). ~~Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE THERAPIES.~~ It is the intent of the HERC that compression dressings and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

Treatment of Hepatitis C with Newer Agents

Question: As new treatment options have emerged for Hepatitis C, what guideline adjustments need to be addressed for this diagnosis on the Prioritized List?

Question source: Medical Directors from CCOs

Issue: The CCO Medical Directors have expressed many concerns about the hepatitis C drugs which have recently become available and the population impact of the tremendous cost that this represents to the plans. These concerns are reiterated through national media and professional discussions, and the Medicaid Evidence-based Decisions project collaboration of 12 states. The CCO Medical Directors have asked HERC to evaluate the prioritization of hepatitis C treatments as well as coverage criteria. The Pharmacy and Therapeutics Committee has updated and revised its PA criteria for the treatment of hepatitis C, following a drug review and after considering the "community standard" recommended by the hepatologists at their March 15th meeting.. It is also developing and adopting a "readiness to treat" document. The HERC last looked at Hepatitis C treatment and guidelines in 1999.

Clinical background from MED 2014:

> "Hepatitis C is estimated to affect between 1% and 2% of the US population. Although up to one quarter of those infected can clear the virus spontaneously, in those remaining infected it can progress over the span of 10 to 30 years or more to cirrhosis, liver failure, HCC and death. The genotype HCV-1 accounts for about three-quarters of cases in the US.

Table 1. Progression of Hepatitis C Virus Infection (CDC 2014)

Condition	Percentage of Patients Who Develop Condition
Chronic HCV infection	75% to 85%
Chronic liver disease	60% to 70%
Cirrhosis over 20 to 30 years	5% to 20%
Death from cirrhosis or liver cancer	1% to 5%

Hepatitis treatments prior to 2011

- The first treatments for hepatitis C became available in the late 90's:
  - Initial treatment involved one year of monotherapy with interferon (PEG-INF or PEG)
  - Within a year the standard treatment became combination therapy for six months, adding ribavirin (RBV) to the regimen (~$17,000 at today's costs)

- Taking interferon produces flu-like symptoms for the duration of the treatment which often leads to discontinuation of therapy,as many of these individuals are otherwise asymptomatic

Newer treatments available since 2011

- A new group of drugs, direct acting antivirals (DAAs), began receiving FDA approval in 2011
- The first of the DAAs, two protease inhibitors -- boceprevir (BOC) and telaprevir (TVR), are given in combination with interferon and ribavirin for type 1 are given over a treatment of 44 weeks, with total costs per treatment of $46,000-$85,000

Table 2. Standard of Care Treatment Regimens (US Department of Veterans Affairs 2013)

Genotype	Treatment	Approximate SVR24 Rate
HCV-1	Double therapy PEG-IFN alfa-2a or alfa-2b weekly + RBV daily for up to 48 weeks	45%
	Triple therapy PEG-INF alfa-2a OR alfa-2b weekly + RBV daily for up to 48 weeks depending on treatment response and either BOC or TVR. BOC is added during weeks 8 to 32 depending on treatment response and TVR is given with PEG-INF and RBV during first 12 weeks of treatment.	65% to 70%
HCV-2	PEG-INF weekly + RBV daily for up to 24 weeks	75%
HCV-3	PEG-INF weekly + RBV daily for up to 24 weeks	75%

- Newer DAAs, sofosbuvir (marketed as Sovaldi), a nucleotide polymerase inhibitor, and simeprevir (marketed as Olysio), a third protease inhibitor, received FDA approval in December 2013
  - Sofosbuvir involves treatment lasting only 12 or 24 weeks, depending on the genetic type of hepatitis C being treated (and it can be used to treat all six genotypes)
    - Current treatment protocols call for sofosbuvir to be used in combination with interferon and ribavirin in most patients, so side effects are still experienced, but over a shorter period of time
      - Interferon not required to treat patients with the less common genotypes 2 and 3
      - Being used in combination with simeprevir as off-label treatment for those not able to take interferon
    - Priced at $1,000 a pill, resulting in retail costs of $84,000 per treatment regimen for a 12-week regimen (in additional to cost of other drugs used) or $168,000 if interferon ineligible

        - Of clinical trials that included FDA-approved treatment regimens, SVR-12 (new measure of sustained viral response 12 weeks post-treatment allowed by FDA) was achieved in 82-95% of patients who had not undergone previous treatment and had other characteristics that made their response to treatment more likely
        - A single smaller study in a more representative population achieved SVR-12 in only 68% of patients
        - 4-18% of patients relapsed in the studies with response-favorable populations, 28% relapsed in the study with a more realistic population (relapsers showed good response at the end of the treatment course but did not achieve SVR at 12 weeks post-treatment)
        - No head-to-head studies with the standard of care to show how it compared
    - Simeprevir is FDA approved for treating genotype 1 when used in combination with interferon and ribavirin for 12 weeks (followed by 12-36 weeks of interferon and ribavirin alone)
        - Also not studied head-to-head with standard of care
        - Pooled data showed an 84-85% SVR-12 in the most favorable subpopulations
        - Pooled data for subpopulations with less favorable characteristics (e.g., previous treatment failure, advanced liver disease, a particular subgroup of genotype 1a) ranged from 45-86% SVR-12 or SVR-24 rates (the outcome measured depending on the study)
        - Pooled relapse rates varied from 6-20% depending on the subpopulation studied
- Evidence will be rapidly emerging and additional new drugs are expected to be approved for use in late 2014
    - Preliminary studies indicate combinations of DAAs will likely result in higher cure rates, but at higher costs

<u>Costs:</u>

- About 5,600 OHP clients are known to have hepatitis C; there are likely more than 13,000 additional clients who do not know they are infected
- The new drug sofosbuvir is $1,000 a pill.
- Expected costs to OHP (FFS +CCO) = $168 million over the next 12 months (assuming only treating those with stage 3 and 4 disease which is approximately 30% of the hep C population)
- Costs to all state programs are estimated to be approximately $250 million, with current P&T restrictions in place

Comments from one medical director:

> "By one calculation, if we took all the dollars we currently spend on Pharmacy in Oregon in Medicaid and dedicated them solely to Hep C, we would only be able to treat 25% of the currently diagnosed Hep C population… with no money left for anything else. If this is even close to true, the consequences are enormous. I believe someone said that California Medicaid plans have said they will not cover the drug until there is some way to pay for it."

At the national level discussions abound:

- National economists are discussing this being a "tipping point" for pharmaceutical pricing. Concern that this will set the bar on pricing of these types of drugs, and if allowed to proceed, lead to even higher pricing.
- Challenges for states and purchasers of healthcare to afford the new treatment options.
- Discussions of how drug prices could be better negotiated, issues of transparency of pricing
- Discussions of whether to cover the new treatments
- Discussions of potentially significantly limiting coverage

Current List Placement:

Line:	**205**
Condition:	CHRONIC HEPATITIS; VIRAL HEPATITIS (See Guideline Notes 64,65)
Treatment:	MEDICAL THERAPY
ICD-9:	070.0-070.1,070.20-070.9,571.40-571.49,571.8-571.9,573.0
CPT:	96150-96154,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375, 99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS:	G0396,G0397,G0406-G0408,G0425-G0427,G0463

Line:	**333**
Condition:	CIRRHOSIS OF LIVER OR BILIARY TRACT; BUDD-CHIARI SYNDROME; HEPATIC VEIN THROMBOSIS; INTRAHEPATIC VASCULAR MALFORMATIONS; CAROLI'S DISEASE (See Coding Specification Below) (See Guideline Note 76)
Treatment:	LIVER TRANSPLANT, LIVER-KIDNEY TRANSPLANT
ICD-9:	277.03,453.0,571.2,571.5-571.6,573.5,751.62,774.4,777.8,996.82,V59.6
CPT:	47133-47147,50300,50323-50365,76776,86825-86835,96150-96154
	Liver-kidney transplant only covered for a documented diagnosis of Caroli's disease (751.62).

Line:	**340**
Condition:	CANCER OF LIVER (See Guideline Notes 7,11,12,33,64,65,76,78)
Treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-9:	155.0,155.2,197.7,235.3,284.11,V10.07,V58.0,V58.11
CPT:	32553,36260-36262,37243,37617,43274-43277,47120-47130,47370,47371,47380-47382,47562,47600-47620,47711,47712,48150,49411,77014,77261-77295,77300-77327,77331-77370,77402-77417,77424-77432,77469,77470,79005-79440,96150-96154,96405,96406,96420-96450,96542-96571,98966-98969, 99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449, 99471-99476,99487-99496,99605-99607
HCPCS:	G0396,G0397,G0406-G0408,G0425-G0427,G0463,S9537

Line: **360**
Condition: ALCOHOLIC FATTY LIVER OR ALCOHOLIC HEPATITIS, CIRRHOSIS OF LIVER (See Guideline Notes 64,65,76,77)
Treatment: MEDICAL THERAPY
ICD-9: 571.0-571.3,571.5-571.6,572.2-572.3,572.8,573.8
CPT: 37182,37183,96150-96154,97802-97804,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

Line: **644**
Condition: OTHER VIRAL INFECTIONS, EXCLUDING PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS IN PERSONS UNDER AGE 3 (See Guideline Notes 61,64,65)
Treatment: MEDICAL THERAPY
ICD-9: 051.01-051.02,052.0-052.9,055.0-055.2,055.71-055.9,056.79-056.9,057.0-057.9,058.10-058.12,059.00-059.9,072.0-072.3,072.71-072.9,074.0-074.1,074.20-074.8,078.0,078.2,078.4-078.7,078.81-078.89, 079.0-079.4,079.50-079.6,079.83-079.99,480.0-480.9
CPT: 98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412, 99429-99449,99471-99476,99487-99496,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

Evidence Review

MED, 2014

1. Rapid evidence review for the Medicaid Evidence based Decisions project, a collaboration of 12 states
2. 10 studies in 7 articles – majority non-comparative, 9 with a high risk of bias. 2 were comparative of sofosbuvir for HCV-2 and HCV-3 infection (neither comparing against standard treatment). No comparative studies for HCV-1.
3. Results of published studies:

FDA Approved Treatment Regimens and Response Rates					
Genotype	**Treatment**	**SVR12**	**Relapse**	**# of Studies (Study name)**	**Study N**
HCV-1	SOF+PEG+RBV 12 w	89%	4% to 8.6%	2 (NEUTRINO, ATOMIC)	379
	SOF+RBV 24 w	68%	28%	1 (Osinusi, NIH Study)	60
HCV-2	SOF+RBV 12 w	82% to 95%	5% to 18%	4 (FISSION, FUSION, POSITRON, VALENCE)	1051
HCV-3	SOF+RBV 24 w	84%	14%	1 (VALENCE)	250

MED, 2014 (Cont'd)

4. Potential concerns about the evidence
    a. Relapse rate may be substantial ranging from 5% to 28%, even among patients who are fully treated with these regimens.
    b. Adverse effects not well studied
5. Patient exclusion criteria from published sofosbuvir trials
    a. Age less than 18 years
    b. HIV or HBV co-infection
    c. Significant alcohol or drug use within the past 12 months
    d. Excessive current alcohol use
    e. Significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, significant renal disease (estimated glomerular filtration rate less than 60mL/min)
6. Conclusions: Based on the usual standards of comparative effectiveness research, currently available studies do not provide sufficient evidence for the routine use of sofosbuvir-containing regimens for the treatment of Hepatitis C infection.
7. If coverage is chosen, potential criteria to guide the use of sofosbuvir that are consistent with current published studies are listed below with several factors to consider.
    a. Limit use to genotypes 2 and 3, until comparative trials available for genotype 1.
    b. Do not use sofosbuvir as monotherapy.
    c. Limit use to patients who failed or did not tolerate current standard of care regimens or in whom PEG is contraindicated.
    d. Confirm degree of liver fibrosis or cirrhosis prior to authorizing treatment.
    e. Treat only patients at greatest risk of progressing to cirrhosis (e.g., Metavir fibrosis stage greater than or equal to 2 and additional factors increasing risk of progression to cirrhosis [e.g., hepatic steatosis, men, older, elevated serum alanine transaminase, greater hepatic inflammation]).
    f. Consider use for patients with HIV or HBV co-infection or those post-liver transplant carefully until comparative trials are available.
    g. Exclude use in patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease (estimated glomerular filtration rate less than 60mL/min).
    h. Ensure that patients who start therapy are closely tracked to optimize full treatment and follow-up, including prevention of re-infection.

Recommendations and considerations by others

OREGON PHARMACY AND THERAPEUTICS COMMITTEE

- The State's Pharmacy &Therapeutics (P&T) Committee has developed prior authorization criteria to restrict coverage of the new drugs to those fee-for-service OHP clients who have hepatitis C with advanced liver disease
  - Limits treatment to patients with advanced liver disease (stage 3 or 4 fibrosis). See Prior Authorization document.
  - A "Readiness to Treat" protocol is under development to assure patients will have the best treatment outcomes possible (by improving treatment adherence and cure rates)

WASHINGTON STATE APPROVAL OF 4/30/14

1. Washington Medicaid will cover hepatitis C treatment when the following criteria have been met:
   a. Metavir Fibrosis Score of ≥F3
      i. Biopsy or fibroscan/FibroSure ≥ F3
      ii. APRI (AST to platelet ratio index) ≥ 1.5
      iii. Abdominal imaging suggestive of cirrhosis
   b. Prescriber is a gastroenterologist, hepatologist or infectious disease specialist, or prescriber is participating in and consults with Project ECHO
2. Patients with the following conditions are not eligible for treatment
   i. Decompensated liver disease as defined by Child-Pugh classification score ≥ 7 (Child Class B or C)
   ii. Patients with alcohol dependence as defined by DSM-IV criteria or moderate or severe alcohol use disorders as defined by DSM-5 who have been in remission for less than 6 months. Exceptions will be considered for patients in remission for 3 months if they are:
      A. Receiving treatment through a DBHR approved facility; or
      B. under the care of an Addiction Medicine specialist.

      Documentation supporting these exceptions will be required.
   iii. Patients with current IV drug use or use within the last 6 months are not eligible for treatment. Exceptions will be considered for patients without use for 3 months if they are:
      A. Receiving opiate substitution therapy through a DBHR approved facility; or
      B. Receiving medication assisted treatment (MAT) from an Addiction Medicine specialist or a buprenorphine waived provider

      Documentation supporting these exceptions will be required

WASHINGTON STATE APPROVAL OF 4/30/14 (Cont'd)

iv. Creatinine Clearance <30
v. Pregnant
vi. Recurrent hepatitis C infection post-liver transplant

3. Recommended Treatment for Eligible Patients:
    a. Genotype 1a/1b: eligible for treatment
        i. naïve patients– sofosbuvir + PEG interferon/RIB for 12 weeks
        ii. PEG/RIB treatment experienced patients–
            A. Relapser - sofosbuvir + PEG interferon/RBV for 12 weeks
            B. Partial Responder or Non-responder - sofosbuvir x 12 weeks + PEG interferon/RBV x 12-24 weeks
        iii. Pre-transplant HCC patients – sofosbuvir + RBV up to 48 weeks or until liver transplantation
    b. Genotype 2:
        i. naïve patients – sofosbuvir + RBV for 12 weeks
        ii. experienced patients - sofosbuvir + RBV for 12 weeks
    c. Genotype 3:
        i. naïve patients – sofosbuvir + RBV for 24 weeks
        ii. experienced patients sofosbuvir + PEG-interferon + RBV for 12 weeks
    d. Genotype 4:
        i. sofosbuvir + PEG-interferon + RBV for 12 weeks
4. Interferon ineligible or intolerant patients, and patients who have previously failed triple therapy (PEG interferon & ribavirin + boceprevir/telaprevir) will be considered on the basis of information submitted by the prescriber. Such information should support efficacy of current available treatments for the client over delaying treatment in favor of potentially more effective regimens expected to become available within the next 24 months.
    a. Interferon ineligible or intolerant criteria:
        i. Platelet count <75,000
        ii. Severe mental health conditions that may be exacerbated by interferon
        iii. Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation
        iv. Inability to complete a prior treatment course due to documented interferon-related adverse effects

VETERANS ADMINISTRATION CONSIDERATIONS (see separate packet document)

Table 2. Considerations for Selecting Chronic HCV-Infected Patients for Treatment

Liver Disease Category	Considerations	Evidence Grade
No cirrhosis	Consider waiting until better treatments are available. Future treatments are likely to have fewer side effects, shorter duration, higher efficacy, and lower pill burden.	B-III
Compensated cirrhosis	Treatment is recommended for appropriate patients with compensated cirrhosis. Refer to Table 13, "Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates," for guidance on diagnosis of cirrhosis.	B-III
Decompensated cirrhosis, defined by one of the following: CTP score ≥7, ascites, hepatic encephalopathy, variceal bleeding or jaundice	Treatment options are limited and the risk versus benefits of treatment must be carefully considered. Consult a specialist with experience in management of HCV.	A-II
Hepatocellular carcinoma (HCC)	Consider treatment for patients in whom HCC treatment is potentially curative, including selected patients on the liver transplant list.	A-II
Post-transplant recipients with cirrhosis	Risk versus benefits of treatment must be carefully considered. Consult a specialist with experience in management of HCV.	A-II
Patients with serious extra-hepatic manifestations of HCV	Patients with serious extra-hepatic manifestations of HCV, such as leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, or symptomatic cryoglobulinemia despite mild liver disease should receive treatment as soon as possible. Consult a specialist with experience in management of HCV.	A-III

CTP = Child-Turcotte-Pugh

SELECTED PRIVATE PAYERS FROM MED REPORT

Payer	Prior Authorization	Approved for all FDA Indications	Notes
Aetna	Yes	Yes	Allows for simeprevir and sofosbuvir combination treatment for genotype 1 PEG ineligible or non-responder
CareMark	Yes	Yes	Excludes ESRD, decompensated cirrhosis, post liver transplant, or significant or unstable cardiac disease

Payer	Prior Authorization	Approved for all FDA Indications	Notes
Cigna	Yes	Unclear	PA form requests information but does not list approval criteria
Anthem/Express Scripts	Yes	Yes	Requires compensated liver disease including cirrhosis
Health Net	Unclear	Yes	Requires liver biopsy showing fibrosis Metavir score ≥ 2 or Ishak score ≥ 3 Policy states that treatment is not authorized for "treatment regimen that patient who has failed therapy with an NS3/4A protease inhibitor (e.g., boceprevir, simeprevir, telaprevir)." Not authorized for post-liver transplant Explicitly excludes simeprevir and sofosbuvir combination treatment
Humana	Yes	No	Requires compensated liver disease Genotype 1 without HIV or HCC requires prior treatment failure with PI triple therapy Approved for all other FDA indications

Abbreviations: ESRD – end-stage renal disease; HIV – human immunodeficiency virus; HCC – hepatocellular carcinoma; PA – prior authorization; PI – protease inhibitors

Note: Private payer policies state coverage subject to individual member benefit contracts.

Guidelines

American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Hepatitis C Guidance (AASLD 2014)

1. Only guideline on treatment
2. Methodologic quality: Poor
    a. Multiple conflicts of interest. Unclear how these were addressed.
3. Includes 27 recommended treatment regimens based on HCV genotype, prior treatment, and co-morbid conditions and nine alternative treatment regimens. All 27 recommended regimens include sofosbuvir except in patients with severe renal impairment.
4. It was published without key sections (coming soon) on:
    • In whom and when to initiate treatment;
    • Monitoring patients who are on or have completed therapy

Treatment of Hepatitis C with Newer Agents

ICER, 2014

1. Comparative clinical effectiveness and value of sofosbuvir and simeprevir
    a. Technology assessment
    b. The costs for initial treatment regimens including sofosbuvir or simeprevir: $88,000 to > $175,000 per patient. Estimate for CA that replacing current care with simeprevir and sofosbuvir-based regimens would raise drug expenditures by $22-33 billion in a single year
    c. Incremental cost required to achieve one additional SVR with newer treatment regimens is greater than $300,000.
    d. Roundtable discussion, with the following policy implications:
        i. Despite having voted that the evidence is adequate to demonstrate the superior clinical effectiveness of the new drugs in most patient subpopulations, the CTAF Panel emphasized in discussion that serious limitations in the evidence base remain.
        ii. For most patient subpopulations, the CTAF Panel found the new drug treatments for hepatitis C to represent a "low value" due to the magnitude of the potential impact on health care budgets of treating large numbers of patients with these high-priced drug regimens.
        iii. Because the financial impact of using these new drugs to treat all eligible patients with hepatitis C is untenable, policy makers should seek avenues to achieve reductions in the effective price of these medications.
        iv. In recognition of limitations of the clinical infrastructure for initiating treatment among a very large patient population, patients, physicians, and payers should work together to encourage informed, shared decision-making about whether patients need to initiate treatment immediately or whether they are well enough to postpone treatment.
        v. Given the limited number of experienced treating clinicians, the balance of risks and benefits for immediate treatment of patients without significant liver damage, and the financial impact of current high prices, it is reasonable to consider prioritization of treatment by level of liver fibrosis.
        vi. Additional policy measures to increase the likelihood of clinical benefit from treatment while reducing the financial impact should be considered. Payers seeking to achieve these goals should consider developing prior authorization criteria that
            1. require patient commitment to and compliance with the treatment regimen,
            2. utilize "futility rules" that define when a lack of early response should lead to discontinuation of treatment, and

ICER, 2014 (Cont'd)

3. require that prescriptions of simeprevir and sofosbuvir be written by specialist physicians with experience treating patients with hepatitis C.

vii. Although there is very little evidence regarding the off-label use of simeprevir and sofosbuvir in combination to treat interferon-ineligible genotype 1 patients, payers may wish to consider covering these drugs on a limited basis for certain patients needing immediate treatment.

viii. Specialty society clinical guidelines should be developed using best practices**,** including ratings of strength of evidence, transparency regarding the role of various organizations involved in guideline development, and full transparency regarding potential conflicts of interest of individual guideline committee members, with limits on the proportion of committee members who receive direct or indirect financial support from manufacturers.

ix. Further evidence should be generated to evaluate more fully the comparative clinical effectiveness and value of these new treatment regimens for patients with hepatitis C.

Summary

Hepatitis C is a very slowly progressive disease. Most patients who have it will never progress to cirrhosis. While the new treatment option of these new DAAs are being put forth as having great promise in treating this disease, the evidence quality is still poor and the cost is extraordinary. The cost could potentially devastate the OHP budget.

Three potential options are proposed for discussion. One is to use prioritization to place this treatment on the lower portion of the Prioritized List based on the poor quality data to support it and the low value. Second is to not make a prioritization decision but simply refer to the P&T criteria to limit use to those for which there is greatest chance of benefit based on disease and patient characteristics. Third, is to refer to P&T criteria, and add additional criteria to further restrict use based on the evidence, or lack thereof.

Treatment of hepatitis C with these newer agents will likely need to be revisited based on the rapid development of the evidence base and new therapies likely to enter the market shortly.

Another issue relates to the lack of longer term outcomes. There is not data about SVR24, instead studies focus on SVR12. One option is to require evidence development as part of coverage to understand better if the outcomes in the OHP population (and perhaps across the state) reflect the initial promising studies.

Prioritization Options:

The following options are presented for discussion. Staff recommendations that include a combination of these options appear at the end of this document:

1) Add hepatitis C codes to Line 644 and add a guideline denoting that new low value agents are included on this Line.
    a. Add the following codes to Line 644. OTHER VIRAL INFECTIONS, EXCLUDING PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS IN PERSONS UNDER AGE 3

ICD-9 Code	Description
070.44	Chronic hepatitis C with hepatic coma
070.49	Other specified viral hepatitis with hepatic coma
070.51	Acute hepatitis C without mention of hepatic coma
070.54	Chronic hepatitis C without mention of hepatic coma
070.59	Other specified viral hepatitis without mention of hepatic coma
070.6	Unspecified viral hepatitis with hepatic coma
070.70	Unspecified viral hepatitis C without hepatic coma
070.71	Unspecified viral hepatitis C with hepatic coma
070.9	Unspecified viral hepatitis without mention of hepatic coma
571.40	Chronic hepatitis, unspecified
571.41	Chronic persistent hepatitis
571.49	Other chronic hepatitis
571.8	Other chronic nonalcoholic liver disease
571.9	Unspecified chronic liver disease without mention of alcohol
571.5	Cirrhosis of liver without mention of alcohol

ICD-10 Code	Description
B18.2	Chronic viral hepatitis C
B18.8	Other chronic viral hepatitis
B18.9	Chronic viral hepatitis, unspecified
B19.0	Unspecified viral hepatitis with hepatic coma
B19.20	Unspecified viral hepatitis C without hepatic coma
B19.21	Unspecified viral hepatitis C with hepatic coma
B19.9	Unspecified viral hepatitis without hepatic coma
K73.0	Chronic persistent hepatitis, not elsewhere classified
K73.1	Chronic lobular hepatitis, not elsewhere classified
K73.2	Chronic active hepatitis, not elsewhere classified

Prioritization Options (Cont'd)

K73.8	Other chronic hepatitis, not elsewhere classified
K73.9	Chronic hepatitis, unspecified
K74.0	Hepatic fibrosis
K74.1	Hepatic sclerosis
K74.2	Hepatic fibrosis with hepatic sclerosis
K74.60	Unspecified cirrhosis of liver
K74.69	Other cirrhosis of liver

b. Add a guideline:
GUIDELINE NOTE XXX, HEPATITIS C
Lines 205, 360, *644*

Pharmacotherapy for hepatitis C infection with oral direct acting antivirals that received FDA approval after 2012 are included only on line 644.

2) Add a guideline limiting treatment of hepatitis C with new oral direct acting antivirals to those that meet specific criteria, referencing P&T criteria and readiness to treat criteria.

GUIDELINE NOTE XXX, HEPATITIS C
Lines 205, 360
Pharmacotherapy for treatment of hepatitis C is included on this line only when the patient meets criteria for use as defined by the Pharmacy and Therapeutics Committee (P&T) according to OAR 410-121-0400 as found in the Sofosbuvir and Hepatitis C Oral Protease Inhibitors/Triple Therapy sections of the Prior Authorization Approval Criteria Guide at http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pa-criteria.pdf.

3) Add a guideline as in Number 2, PLUS *(some or all of the following):*
   a. Candidates for the newer oral direct acting antivirals
      A. MUST ALSO:
         1. Have failed or did not tolerate current standard of care regimens or in whom PEG is contraindicated
         2. Be closely tracked to optimize full treatment and follow-up, including prevention of re-infection.
         3. Have genotype 2 or 3
         4. Be 18 or older
         5. Demonstrate early responsiveness to treatment for treatment to be continued
         6. Demonstrate ongoing compliance

Prioritization Options (Cont'd)

7. Be receiving medications through a physician with specialist training in hepatitis C treatment

B. MUST NOT:
1. Be at risk of reinfection
2. Be using sofosbuvir as monotherapy
3. Be co-infected with HBV or HIV
4. Be post-liver transplant
5. Have genotype 1
6. Have had alcohol or drug use within the past 6-12 months
7. Have significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease (estimated glomerular filtration rate less than 60mL/min).
8. Have decompensated liver disease as defined by Child-Pugh classification score ≥ 7 (Child Class B or C)
9. Have had previous treatment with an oral direct acting antiviral that was FDA approved after 2012

HERC Staff Recommendations:

Based on the existing evidence, and particularly that analyzed by a trusted source (the May 2014 MED report), staff recommends a combination of the above options as follows:

1. Add the hepatitis C ICD-9 and ICD-10 codes as identified in Option #1a to Line 644, OTHER VIRAL INFECTIONS, EXCLUDING PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS IN PERSONS UNDER AGE 3, accompanied by the following guideline:

GUIDELINE NOTE XXX, HEPATITIS C

Lines 205, 360, 644

Pharmacotherapy for hepatitis C is included on Lines 205 and 360 only when using prescription drugs receiving FDA approval for the treatment of hepatitis C prior to 2012.

Pharmacotherapy for treatment of hepatitis C is included on Line 644 when the patient meets criteria for use as defined by the Pharmacy and Therapeutics Committee (P&T) according to OAR 410-121-0400 as found in the Sofosbuvir and Hepatitis C Oral Protease Inhibitors/Triple Therapy sections of the Prior Authorization Approval Criteria Guide at http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pa-criteria.pdf.

HERC Staff Recommendations (Cont'd)

Furthermore, candidates for the use of oral direct acting antivirals that obtained FDA approval after 2012:

A. MUST ALSO:
   1. Be 18 or older
   2. Demonstrate early responsiveness to treatment for treatment to be continued
   3. Demonstrate ongoing compliance
   4. Be receiving medications through a physician with specialist training in hepatitis C treatment
   5. Be determined to be appropriate candidates for treatment based on demonstrated ability to comply with treatment and appropriate control of comorbid disease
   6. Be closely tracked to optimize full treatment and follow-up, including prevention of re-infection.

B. MUST NOT:
   1. Have had previous treatment with an oral direct acting antiviral that was FDA approved after 2012
   2. Be using sofosbuvir or simeprevir as monotherapy
   3. Be post-liver transplant
   4. Have had alcohol or drug use within the past 6 months
   5. Have significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease (estimated glomerular filtration rate less than 60mL/min).
   6. Have decompensated liver disease as defined by Child-Pugh classification score ≥ 7 (Child Class B or C)

2. Consider adding this to the Guideline:
   For all patients who are authorized to receive treatment, an SVR24 must be reported by the manufacturer.
   Note: This would require further conversations within OHA to determine implementation

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Abbreviated Class Update: Hepatitis C

Month/Year of Review: March 2014
Current PDL Class: Hepatitis C Agents

Last Review: September 2013
Source Document: OSU College of Pharmacy

- **Preferred Agents:** BOCEPREVIR (VICTRELIS®), TELAPREVIR (INCIVEK®), SOFOSBUVIR (SOLVALDI®), SIMEPREVIR (OLYSIO®), PEGINTERFERON ALPHA-2A (PEGASYS®), PEGINTERFERON ALPHA-2A SUBQ (PEGASYS®, PEGASYS PROCLICK®), PEGINTERFERON ALFA-2B, PEGINTERFERON ALFA-2B, RIBAVIRIN
- **Non-Preferred Agents**: INTERFERON ALFACON-1 (INGERGEN®), RIBAVIRIN DOSE-PACK (RIBAPAK®)

Current PA: Prior authorizations are currently in place or have been recommended for pegylated interferon and ribavirin (PR), for the oral protease inhibitors, and for sofosbuvir (Appendix 1) to ensure treatments are supported by the medical literature.

Research Questions:
- Is there any new evidence about comparative effectiveness of antiviral regimens, in long term clinical outcomes such as mortality and hepatitis C complications or in sustained virologic response (SVR) in adult patients being treated for chronic Hepatitis C virus (HCV)?
- Is there any new evidence about comparative harms of antiviral regimens in adult patients being treated for chronic HCV?
- Are there subpopulations of patients with HCV for which one antiviral regimen is more effective or associated with less harm?

Conclusions:
- In Genotype 1 treatment naïve patients and treatment experienced patients, there is insufficient to low quality evidence that simeprevir does not appear to significantly improve the SVR12 compared with triple therapy with boceprevir and telaprevir, and its effectiveness is diminished in patients with the Q80K genetic polymorphism in HCV genotype 1. [1] Simeprevir requires peginterferon and ribavirin (PR) and cannot be used to treat interferon-ineligible patients. There is an ongoing randomized trial comparing simeprevir to telaprevir is the first trial directly comparing 2 antiviral agents. Sofosbuvir therapy appears to have the highest SVR12 in this population (83%; 95% CI 79% to 87%).[1]
- There is insufficient evidence to evaluate the use of simeprevir or sofosbuvir in treatment-naïve genotype 1 patients who are interferon-ineligible.
- There is insufficient data to evaluate sofosbuvir plus ribavirin for genotype 1 treatment experienced patients or simeprevir plus PR.
- There is moderate quality evidence that in genotypes 2 and 3 CHC, sofosbuvir-based therapy improves SVR rates compared to dual therapy with pegylated interferon and ribavirin.
- There is low quality evidence, based on one unpublished open-label trial, that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks results in high SVR12 rates (79-96%) in HCV genotype 1 null responders with METAVIR F0-F2 fibrosis.[2]

- There is insufficient evidence that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks is efficacious in HCV genotype 2 treatment naïve and null responder patients with METAVIR F3-F4 fibrosis. Only preliminary data is available demonstrating SVR4 rates of 96-100%; SVR12 rates have not yet been released.[2]
- There is insufficient evidence evaluating the safety and efficacy of simeprevir in HCV patients with moderate or severe hepatic impairment. Clinical trials with simeprevir have been limited to patients with compensated disease who have CTP class A, total bilirubin level of 1.5 ULN or lower, and transaminase level of 10 x ULN or lower. It should be limited to patients with compensated liver disease.
- There is insufficient data evaluating sofosbuvir in patients with severe renal impairment (CrCl <30 ml/min) or those who require hemodialysis. There is no dosing data currently available for this patient population.

Recommendations:

- Recommend revising sofosbuvir prior authorization criteria for appropriate patient selection, including criteria to avoid in patients with significant renal impairment, those with decompensated liver disease, and those who would not be noncompliant for a variety of reasons (Appendix 1).
- Continue to evaluate new evidence as it comes out for further revisions.
- Evaluate comparative costs in executive session for PDL decisions.

Previous Conclusions and Recommendations:

Class Update

- There is moderate strength evidence from a recent AHRQ report of a lower chance of achieving an SVR with dual therapy with pegylated interferon alfa-2b plus ribavirin compared to dual therapy with pegylated interferon alfa- 2a (pooled RR 0.87, 95% CI 0.80 to 0.95; I2=27.4%), with an absolute difference in SVR rates of 8 percentage points, while dual therapy with interferon alfa-2b is associated with a lower risk of serious adverse events than dual therapy with interferon alfa-2a (pooled RR 0.76, 95% CI 0.71 to 0.88; I2=0.0%) with no differences in withdrawals due to adverse events (pooled RR 1.1, 95% CI 0.73 to 1.7, I2=42%).
- There is high quality evidence that triple therapy with either boceprevir or telaprevir produces a higher likelihood of achieving SVR as compared to dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin.
- There is insufficient direct comparative evidence between boceprevir (BOC) and telaprevir (TVR) on long term clinical outcomes**.**

Sofosbuvir

- There is poor quality evidence, based on one open-label trial, that sofosbuvir in combination with ribavirin for 12 weeks is noninferior to pegylated interferon plus ribavirin for 24 weeks in genotype 2 and 3 treatment-naïve chronic Hepatitis C (CHC) in achieving SVR at week 12 (67% for both groups).
- There is moderate quality evidence that sofosbuvir in combination with ribavirin for 12 weeks is superior to placebo in genotype 2 and 3 CHC patients who are intolerant or ineligible for interferon based therapy in achieving SVR at week 12 (78% vs. 0%; p<0.001), as well as in patients who did not have a response to interferon therapy.
- There is evidence that extending the duration of treatment in genotype 3 patients to 24 weeks improves SVR rates compared to 12 weeks of treatment. Across all studies, genotype 2 patients achieved consistently higher SVR rates than genotype 3 patients.
- In genotype 1, there low quality evidence that the combination of sofosbuvir plus ribavirin plus peginterferon alfa results in higher rates of SVR at 12 weeks than historical control rates (90% vs. 60%). This is based on a single arm, open-label study.
- Based on limited data, sofosbuvir appears to have no serious adverse event concerns associated with its use and is well-tolerated for 12-16 weeks. The most common adverse events (>20%) of sofosbuvir in combination with ribavirin were fatigue and headache. The most common adverse events in combination

with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia, and anemia. Overall discontinuations due to adverse events in trials were low (0-2%).

Simeprevir

- There is evidence that simeprevir in combination with peginterferon alfa and ribavirin significantly improves SVR rates compared to placebo in patients with genotype 1 CHC, in both treatment- naïve patients (80% vs. 50%) and treatment experienced (79% vs. 36%, respectively). Most of the data remains unpublished and cannot be assessed for quality.
- There is low quality evidence, based on one phase IIb trial, that simeprevir in combination with peginterferon alfa and ribavirin is effective in achieving SVR in partial and null responders.
- Compared to placebo, there is low quality evidence that simeprevir does not significantly improve SVR rates in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline. Screening patients with HCV genotype 1 for the presence of this polymorphism is strongly recommended and alternative therapy should be considered for patients infected with the Q80K polymorphism.
- There is insufficient evidence evaluating simeprevir in patients who have previously failed therapy with a treatment regimen that includes simeprevir or other HCV protease inhibitors.
- There is insufficient evidence evaluating the use of simeprevir in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).The combination of simeprevir should not be used in patients with decompensated cirrhosis (moderate to severe hepatic impairment).
- There is low quality evidence of an increased risk of adverse reactions in patients of East Asian ancestry due to higher simeprevir exposure.

Reason for Review: New clinical practice guidelines for the treatment of chronic Hepatitis C were recently released. With the approval of the two new oral agents, these guidelines as well as any new evidence within the class will be reviewed for further decision-making.

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.[3] The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer. [3] The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. The studies evaluating sofosbuvir use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.[4]

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients. [3] Current standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.[5] This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to the previous standard of care of pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which can result in serious adverse reactions. There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3,

the standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.[6]

Simeprevir is a recently approved protease inhibitor used in combination with pegylated interferon and ribavirin for the treatment of adult patients with genotype 1 CHC. This includes patients with compensated liver disease, including patients with cirrhosis, who are treatment-naïve or who failed prior interferon therapy with or without ribavirin. There are trials underway evaluating its use in genotype 4 infection and HCV/HIV co-infection. Studies investigating the use of simeprevir as part of interferon-free regimens have also been intiated.[7] Simeprevir structurally binds to a target enzyme which is different than telaprevir and boceprevir (14-membered macrocycle). It is given orally once a day with any type of food for 12-48 weeks depending on whether the patient is treatment-naïve, a prior relapse, or a nonresponder.

Sofosbuvir is a nucleotide inhibitor of HSV NS5B RNA-dependent RNA polymerase with broad genotypic activity. Sofosbuvir was given breakthrough therapy designation as the first potential interferon-free CHC therapy from the FDA that allowed an expedited approval program.[4] The criteria for a breakthrough therapy designation from the FDA is that a) it is used for a serious condition, and b) preliminary clinical evidence demonstrates substantial improvement over available therapy on one more clinically significant endpoints. Unlike the other available protease inhibitors, there is no response guided therapy criteria for its use.

Methods:
A Medline literature search beginning September 2013 (since the most recent Hepatitis C Class Update) and ending February 2014 for new systematic reviews and randomized controlled trials (RCTs) that compared antiviral regimens and oral protease inhibitors, including boceprevir (BOC), telaprevir (TVR), simeprevir (SIM), and sofosbuvir (SOF) was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. The initial literature search resulted in 83 citations. After further review and exclusion of studies with drugs not yet FDA approved or already reviewed in preliminary SIM and SOF reviews, the search resulted in 7 RCTs[8–14], 2 systematic reviews[1,15], and 2 updated clinical practice guidelines.[16,17]

Systematic Reviews:
A draft technology report from the Institute for Clinical and Economic Review (ICER) was published in February 2014.[1] The assessment attempted to answer the following questions: 1) among patients with genotype 1, are treatment regimens incorporating the new DAAs equivalent or superior to the current standard of care, pegylated interferon plus ribavirin and one of the protease inhibitors; 2) among patients with genotypes 2 and 3, is the combination of sofosbuvir and ribavirin equivalent or superior to the current standard of care, pegylated interferon plus ribavirin; and 3) among interferon-ineligible or intolerant patients, is the combination of sofosbuvir plus ribavirin or sofosbuvir plus simeprevir equivalent or superior to no treatment. There were no studies found that directly compared therapies based on simeprevir to those based on sofosbuvir or to the two protease inhibitors boceprevir and telaprevir. A network meta-analysis was done to provide indirect evidence about the relative efficacy for the drug combinations available using these therapies.

The literature search identified 327 potentially relevant studies, resulting in 21 included publications describing simeprevir or sofosbuvir. Due to the paucity of literature, unpublished trials were included as well. All of the studies excluded patients with HIV, hepatitis B, or other significant illnesses. Results from the network meta-analyais for SVR12 among treatment naive patients infected with HCV genotype 1 are included in the following table:

Treatment	SVR12	95% CI	P versus PR
PR	47%	41% to 52%	-
Boceprevir + PR	73%	68% to 77%	<0.001
Telaprevir + PR	74%	69% to 79%	<0.001
Simeprevir + PR	76%	70 to 81%	<0.001
Sofosbuvir + PR	83%	79% to 87%	<0.001

PR: pegylated interferon + ribavirin

This suggests that simeprevir has similar SVR12 results compared to triple therapy with boceprevir or telaprevir and sofosbuvir therapy has the highest estimated SVR12. However, this is based on many assumptions as well from uncontrolled trials and therefore the evidence remains insufficient to make definitive conclusions regarding the comparative effectiveness of the agents. There were no studies for interferon-ineligible patients in treatment naïve patients.

For genotype 1 treatment experienced patients, again SVR 12 for simeprevir based therapy (67%; 95% CI 59-74%) was similar as that for triple therapy with boceprevir (64%; 95% CI 40-76%) and telaprevir (70%; 95% CI 61-77%). The combination of simeprevir plus sofosbuvir had the highest estimated SVR12 (90%; 95% CI 78-96%) but this is based on extrapolations from one uncontrolled trial and therefore the uncertainty of the results remains low. There were no studies in treatment-experienced patients who were interferon-ineligible. However, the combination of simeprevir and sofosbuvir evaluated four interferon-free regimens in treatment-experienced patients. The authors concluded that there is insufficient data to evaluate sofosbuvir plus ribavirin for genotype 1 treatment experienced patients and no data on sofosbuvir plus PR.

For genotype 2, the SVR24 for PR alone has shown to be 75-85%. Of the newer agents, only sofosbuvir has been approved for the treatment of genotypes 2 and 3. In genotype 2 treatment-naïve patients, there were a total of 8 studies (7 in interferon-eligible and 1 in interferon-ineligible). Sofosbuvir demonstrated an improvement in SVR over the previous standard of care, treatment time is decreased from 24 to 12 weeks, and interferon is no longer needed. It has also been studied in patients unwilling, unable, or intolerant of interferon. For treatment-experienced patients none of the trials had a control group without sofosbuvir. For genotype 3 treatment-naïve and treatment experienced patients, 24 weeks of sofosbuvir plus ribavirin appears to be superior to 12 or 16 weeks of the same therapy. The POSITRON data suggest that sofosbuvir plus ribavirin is effective for interferon-ineligible patients with genotype 3 and the VALENCE trial suggests that 24 weeks of therapy would be more effective than 12 weeks.

Overall, the authors noted that the addition of simeprevir to PR did not markedly increase the risk of adverse events. It was more difficult to assess the relative impact of sofosbuvir on adverse events because few of the trials randomized patients to a regimen without sofosbuvir. The most common adverse events in genotype 1 patients on sofosbuvir and PR included fatigue, headache, and flu-like illness and fewer patients stopped therapy due to adverse events than those in the PR group (2% vs. 11%). In genotype 2 and 3 patients, the elimination of interferon from the treatment regimen markedly decreased the risk for most adverse events. There were also significantly fewer grade 3 or 4 adverse events, and a reduction in discontinuation of therapy due to adverse events.

Pegylated Interferon:

A systematic search including randomized, prospective studies compared rapid virological response (RVR) and early virological response (EVR) rates of peginterferon alfa-2a vs. peginterferon alfa-2b.[15] A total of 8 RCTs were included in the meta-analysis. The early virological response meta-analysis included 7 trials and 4359 patients and showed an overall significant increase in the percentage of patients treated with peginterferon alfa-2a that achieved EVR when compared with the peginterferon alfa-2b group (53.3% vs. 43.8%; p=0.0028). The meta-analysis of RVR included 5 trials and 3833 patients with an estimated effect in favor of peginterferon alfa-2a of 25% vs. 16.8% for peginterferon alfa-2b (p=0.0056).

Clinical Guidelines:

On January 29, 2014, the American Association for the Study of Liver Diseases (AASLD) / Infectious Diseases Society of America (IDSA) / International Antiviral Society (IAS) jointly created guidelines for the treatment of chronic hepatitis C.[17] The Guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases, but did lack non-specialist members. Recommendations were graded in terms of the level of the evidence and strength of the recommendation, using a scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. The main recommendations are as followed:

Treatment naïve or those who experienced relapse after prior treatment with peginterferon and ribavirin:

Genotype 1, interferon eligible

1. Initial therapy with sofosbuvir plus PR for 12 weeks (Class 1, Level A recommendation).
    a. This is based on one poor quality, open-label, single-arm phase 3 NEUTRINO trial evaluating sofosbuvir in combination with pegylated interferon and ribavirin in 291 treatment-naïve patients with HCV genotype 1 infection. The SVR 12 was 89% and was lower in patients with cirrhosis.
2. Alternative regimens include daily simeprevir + PR for 12 weeks (for only those with HCV genotype 1b or HCV genotype 1a without the Q80K polymorphism). (Class IIA, Level A recommendation).
    a. The alternative regimen is based on two unpublished, randomized, placebo controlled phase 3 trials evaluating the efficacy and safety of simeprevir
3. Treatment with telaprevir or boceprevir is NOT recommended (Class IIB, Level A recommendation).
4. Monotherapy with pegylated interferon, ribavirin, or a direct acting antiviral are not recommended (Class III, Level A recommendation).

Genotype 1, interferon ineligible

1. Sofosbuvir plus simeprevir, with or without ribavirin for 12 weeks is recommended (Class I, Level B recommendation)
    a. This is based on the unpublished ongoing phase 2 COSMOS trial. This regimen should only be considered in patients who require immediate treatment.
2. Alternative regimen of sofosbuvir plus ribavirin for 24 weeks (Class IIb, Level B recommendation).
    a. This is based on one, poor quality, phase 2, open-label clinical trial in 60 treatment-naïve patients with unfavorable characteristics (African American race and advanced fibrosis).

Genotype 2

1. Sofosbuvir plus ribavirin for 12 weeks (Class I, Level A recommendation). There are no recommended alternative regimens.
    a. This is based on 2 fair quality and one unpublished phase 3 trials. Across all 3 trials, 94% of patients achieved SVR with sofosbuvir plus ribavirin.

Genotype 3

1. Sofosbuvir plus ribavirin for 24 weeks (Class I, Level B recommendation)
    a. One unpublished trial (VALENCE) demonstrated that higher response rates can be achieved with a 24-week duration of sofosbuvir than those reported for the 12 or 16 week durations studied in other trials (84% vs. 61%, respectively).
2. Alternative regimen is sofosbuvir plus ribavirin plus peginterferon alfa for 12 weeks.
    a. Two unpublished trials (PROTON and ELECTRON) have evaluated the combination of sofosbuvir + PR in patients with genotype 3 HCV and demonstrated a 97% SVR rate in treatment-naïve patients. This regimen has a higher risk of adverse effects and may require increased monitoring.

Genotype 4, interferon eligible

1. Sofosbuvir + PR is recommended for 12 weeks (Class IIa, Level B recommendation). Few data is available for genotype 4 and only patients who immediate treatment is required should be treated.
    a. This is based on one poor quality, open-label, single arm study (NEUTRINO) evaluating 12 weeks of sofosbuvir. Of the 28 patients with genotype 4, 27 (96%) achieved SVR12.
2. Alternative regimen of simeprevir for 12 weeks plus ribavirin and peginterferon for 24-48 weeks is recommended (Class IIB, level B recommendation).
    a. This is based on one ongoing phase 3 trial in patient with genotype 4.

Genotype 4, interferon ineligible

1. Sofosbuvir plus ribavirin for 24 weeks is recommended (Class IIB, Level B recommendation).
    a. This is based on a small, unpublished study of Egyptian patients in the U.S. treated with sofosbuvir plus ribavirin. SVR 12 was achieved in 11 of 14 (79%) treatment-naïve patients treated for 12 weeks. SVR24 was achieved in 100% of the 14 treatment-naïve patients treated for 24 weeks.

Retreatment of persons in whom prior therapy has failed (non-responders, including null responders and partial responders):

Genotype 1 nonresponders

1. Initial therapy with sofosbuvir plus simeprevir, with or without ribavirin for 12 weeks (Class IIA, Level B recommendation).
    a. This is based on the unpublished, phase 2a, randomized trial (COSMOS) evaluating the combination of sofosbuvir plus simeprevir with or without weight based ribavirin for 12 or 24 weeks. Of the 80 null responders with a Metavir fibrosis stage of 2 or less, 79% to 96% achieved SVR. Among those null responders with a Metavir fibrosis stage of 3 or 4 (n=47), SVR4 was observed in 93% of the 15 patients in the ribavirin containing arm and 100% of the 7 participants in the ribavirin-free arm. SVR 12 data is not yet available for this cohort of patients. This should not be used in those who have had previous treatment with either telaprevir or boceprevir.
2. Alternative regimens include daily sofosbuvir for 12 weeks and PR for 12-24 weeks (Class IIB, Level C recommendation).
    a. The alternative regimen is based on very limited data, including a poor quality, single arm, open-label trial (NEUTRINO) that evaluated 12 weeks of sofosbuvir in treatment-naïve subjects. Although treatment-experienced subjects were not included in this study, FDA estimates that the response rate in such patients would approximate the observed response rate in those in the NEUTRINO trial with baseline factors traditionally associated with a lower response to interferon-based treatment.
3. Alternative regimen includes simeprevir for 12 weeks plus PR for 48 weeks; all patients with cirrhosis who are receiving simeprevir should have well compensated liver disease (Class IIa, Level A recommendation).
    a. The ASPIRE trial is a phase 2b recently published trial evaluating simeprevir + PR in patients who had previously failed to respond to dual therapy.[14] SVR24 after 48 weeks of triple therapy in the simeprevir 150 mg/day arm was 65% in patients with a previous partial response (n=23) and 53% in patients with a prior null response (n=17).

4. Treatment with telaprevir or boceprevir is NOT recommended (Class IIB, Level A recommendation).

Genotype 2, nonresponders

1. Sofosbuvir + ribavirin for 12 weeks; patients with cirrhosis may benefit by extension of treatment to 16 weeks (Class 1, Level A recommendation).
2. Sofosbuvir + PR for 12 weeks (Class IIa, Level B recommendation).
    a. The LONESTAR-2 trial is an unpublished, open-label, single site, single-arm phase 2 trial evaluating triple therapy with sofosbuvir in treatment-experienced patients with HCV genotype 2 or 3.

Genotype 3, nonresponders

1. Sofosbuvir plus ribavirin for 24 weeks (Class IIa, Level A recommendation)
2. Alternative regimen includes retreatment with sofosbuvir + PR for 12 weeks.

EASL Clinical Practice Guidelines:

In December 2013, the European Association for the Study of the Liver (EASL) updated its HCV treatment guidelines.[16] These guidelines were developed by a panel of experts and peer-reviewed by external expert reviewers. They were established using evidence and when not available, experts' experiences and opinion. The GRADE system was used to evaluate the strength of recommendations. These guidelines did not include the new agents, sofosbuvir and simeprevir, and are therefore outdated. Relevant guidelines regarding initiation of therapy are included as follows:

- All treatment-naïve patients with compensated disease due to HCV should be considered for therapy (recommendation A1).
- Treatment should not be deferred for patients with significant fibrosis, METAVIR score F3 to F2 (recommendation A1).
- In patients with less severe disease, the indication for and timing of therapy can be individualized (recommendation B1).

Simeprevir and Sofosbuvir Combination Therapy:

There is one small unpublished phase IIa study (COSMOS) evaluating the combination of simeprevir and sofosbuvir in the treatment of previous null responders and treatment naïve patients.[2] Currently, only the abstract is available. The study is an open-label, randomized, phase II study in genotype 1 patients (n=167) with METAVIR scores F0-F2 who were prior null responders to PR (Cohort 1) or treatment-naïve patients and prior null responders with F3-F4 (Cohort 2). Patients in both cohorts were also randomized to simeprevir + sofosbuvir (with or without ribavirin for 12 weeks of simeprevir + sofosbuvir (with or without ribavirin) for 24 weeks. SVR 12 rates in the F0-F2 groups ranged from 79.2% to 96.3%. The lowest SVR 12 was in the most intense (24 weeks of the combination with ribavirin) treatment group and appears to be due to participants lost to follow-up, but the details of the data are not clear at this point. The highest SVR12 rate was in the simeprevir + sofosbuvir + ribavirin for 12 weeks group and SVR 12 was only 88.9% in those with the Q80K polymorphism. The results in the Cohort 2 patients with METAVIR F3-F4 fibrosis scores have not been released yet, although the preliminary SVR4 rates appear high. This preliminary data suggests that there may be no benefit from adding ribavirin to simeprevir and sofosbuvir and that 12 weeks of treatment may results in similar benefits compared to 24 week treatment. The most common adverse events were fatigue, headache, and nausea and anemia occurred mostly in the ribavirin-containing treatment groups.

Randomized Controlled Trials:

Seven potentially relevant RCTs were evaluated from the literature search. After further review, 2 RCTs[8,9] included drugs not yet FDA approved and were therefore excluded, and one was a phase I study of boceprevir in HCV 2 and 3 genotype isolates assays and was also excluded.[10] The remaining 4 RCTs are briefly described in the table below. Abstracts of these trials are found in Appendix 2:

Study	Comparison	Population	Primary Outcome	Results
Zeuzem et al.[14] RCT, Phase IIb, DB, PC	Simeprevir 12-48 weeks + PR vs. PR x 48 weeks	HCV genotype 1, non-responders to dual therapy with peginterferon and ribavirin	SVR at week 24 (SVR24)	<u>SVR24</u> SIM: 60.6%-80% Pla: 22.7% P<0.001 <u>Null responders:</u> SIM: 37.5-58.8% Pla: 18.8% <u>Partial responders:</u> SIM: 47.8%-86.4% Pla: 8.7% <u>Relapsers</u> SIM: 76.9-88.9% Pla: 37%
Liu et al.[11] Open-label, RCT	Pegylated interferon-alfa2a plus ribavirin vs. pegylated interferon alfa2a monotherapy x 48 weeks (n=205)	Treatment-naïve patients with HCV genotype 1 receiving hemodialysis	SVR24	<u>SVR24</u> Peg + Rib: 66/103 (64%) Peg alone: 34/102 (33%) RR 1.92; 95% CI 1.41-2.62 P<0.001
Rodriguez-Torres et al.[12], RCT, DB, dose-ranging	Sofosbuvir (100, 200, or 400 mg) vs. placebo + PR x 28 days, followed by 44 weeks of PR alone	Treatment-naïve, HCV genotype 1, non-cirrhotic	SVR24	<u>SVR24</u> Sof 100: 56% Sof 200: 83% Sof 400: 80% PR: 43% Peg alone: 34/102 (33%) RR 1.92; 95% CI 1.41-2.62 P<0.001
Benhamou et al.[13] Phase 2a, partially blinded, RCT	Telaprevir 750 mg every 8 hours vs. telaprevir + PR vs. PR + placebo x 15 days (n=24)	Treatment-naïve, HCV genotype 4	The effect of telaprevir on early viral kinetics	<u>SVR at the end of treatment</u> Telaprevir: 62.5% Telaprevir + PR: 50% PR: 62.5%

<u>Ongoing Trials:</u>

A randomized trial comparing simeprevir to telaprevir in treatment-experienced patients is underway. This will be the first study to compare the new DAAs to the current standard of care for treating HCV genotype 1.[1]

References:

1. Institute for Clinical and Economic Review (ICER). The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection. Draft Technology Assessment. 2014. Available at: http://ctaf.org/assessments/treatments-hepatitis-c.
2. Jacobsen I, Ghalib R, Rodriguez-Torres M. ABSTRACT: SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1treatment-naïve and prior null responder patients: The COSMOS study. *Hepatology*. 2013;6(58):1379A–1380A.
3. Chou R, Hartung D, Rahman B, Wasson N, Cottrell E, Fu R. *Treatment for Hepatitis C Virus Infection in Adults*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. Available at: http://www.ncbi.nlm.nih.gov/books/NBK115347/. Accessed July 18, 2013.
4. FDA Antiviral Drugs Advisory Committee Meeting. Sofosbuvir (GS-7977) Background Packate. October 25, 2013. Available at:http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/antiviraldrugsadvisorycommittee/ucm371876.pdf.
5. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(4):1433–1444. doi:10.1002/hep.24641.
6. Yee HS, Chang MF, Pocha C, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *Am J Gastroenterol*. 2012;107(5):669–689; quiz 690. doi:10.1038/ajg.2012.48.
7. Simeprevir (TMC435). FDA Antiviral Drugs Advisory Committee Meeting. October 24th, 2013. Background Packate for NDA 205123. Available at: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CC4QFjAA&url=http%3A%2F%2Fwww.fda.gov%2Fdownloads%2FAdvisoryCommittees%2FCommitteesMeetingMaterials%2FDrugs%2FAntiviralDrugsAdvisoryCommittee%2FUCM371623.pdf&ei=8lGvUr-UMsWbygHIr4DoAw&usg=AFQjCNGsHT7v0WZNvYximPhkr9qgFSuhMw&sig2=fKXf_Fo7xTH1FcoXHlmxrQ&bvm=bv.57967247,d.aWc&cad=rja.
8. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med*. 2014;370(3):211–221. doi:10.1056/NEJMoa1306218.
9. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med*. 2014;370(3):222–232. doi:10.1056/NEJMoa1306227.
10. Silva M, Treitel M, Graham D, et al. Antiviral activity of boceprevir monotherapy in treatment-naive subjects with chronic hepatitis C genotype 2/3. *Journal of Hepatology*. 2013;59(1):31–7. doi:http://dx.doi.org/10.1016/j.jhep.2013.02.018.
11. Liu C-H, Huang C-F, Liu C-J, et al. Pegylated interferon-α2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. *Ann Intern Med*. 2013;159(11):729–738. doi:10.7326/0003-4819-159-11-201312030-00005.
12. Rodriguez-Torres M, Lawitz E, Kowdley KV, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. *J Hepatol*. 2013;58(4):663–668. doi:10.1016/j.jhep.2012.11.018.
13. Benhamou Y, Moussalli J, Ratziu V, et al. Telaprevir activity in treatment-naive patients infected hepatitis C virus genotype 4: a randomized trial. *Journal of Infectious Diseases*. 2013;208(6):1000–7. doi:http://dx.doi.org/10.1093/infdis/jit274.
14. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology*. 2014;146(2):430–441.e6. doi:10.1053/j.gastro.2013.10.058.
15. Romero-Gomez M, Planas R, Ampuero J, et al. Meta-analysis: pegylated interferon alpha-2a achieves higher early virological responses than alpha-2b in chronic hepatitis C. *Alimentary Pharmacology & Therapeutics*. 2013;37(11):1065–73. doi:http://dx.doi.org/10.1111/apt.12314.
16. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. *J Hepatol*. 2014;60(2):392–420. doi:10.1016/j.jhep.2013.11.003.
17. American Association for the Study of Liver Diseases / Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C. 2014. Available at: http://www.hcvguidelines.org/full-report-view.

Appendix 1: Prior authorization Criteria

Sofosbuvir (Sovaldi®)

Goal(s) :

- Approve treatments of chronic hepatitis C which are supported by the medical literature and where there is medical evidence of effectiveness and safety

Length of Authorization

- Initial trial of 12 weeks
- Continuation of therapy up to 24-48 weeks of total therapy based on therapy regimen, genotype, and patient population

Requies PA:

- Sofosbuvir

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Is the request for continuation of therapy?	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #3
3. What Hepatitis C genotype is the patient? Record Genotype:	**Record Genotype and go to #4**	
4. Is the patient being prescribed the appropriate concomitant therapy based on genotype as seen in the dosage and administration table on the next page?	**Yes:** Go to #5	**No:** Pass to RPh, Deny For Appropriateness
5. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness
6. If the patient has been treated with peginterferon and ribavirin before, do they have documented noncompliance to their previous treatment?	**Yes:** Pass to RPh, Deny For Appropriateness	**No:** Go to #7
7. Does the patient have a biopsy or other non-invasive technology (Fibroscan) to indicate moderate to severe fibrosis (stage 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins).	**Yes:** Go to #8	**No:** Pass to RPh, Deny For Appropriateness
8. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #9	**No:** Pass to RPh, Deny For Appropriateness
9. Does the patient have a HIV coinfection?	**Yes:** Go to #10	**No:** Go to #11
10. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #11	**No:** Pass to RPh; Deny (medical appropriateness)
11. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?	**Yes**: Go to #12	**No:** Pass to RPh, Deny for appropriateness
12. Does the patient have any of the following contraindications to therapy?	**Yes:** Pass to RPh; Deny for	**No:** Go to #13

• Severe or uncontrolled psychiatric disorder • Decompensated cirrhosis • Pregnancy	appropriateness	
13. Does the patient have significant renal impairment (CrCl < 30 ml/min) or end stage renal disease (ESRD)?	**Yes:** Pass to RPh; Deny for appropriateness	**No:** Go to #14
~~12.~~14. Is the request for sofosbuvir 400 mg daily?	**Yes:** Approve for 12 weeks for initial therapy.	**No:** Pass to RPh; Deny for appropriateness

P&T Board Action: 1/30/13 (MH)
Revision(s): 3/27/13
Initiated:

Continuation of Therapy- Sofosbuvir		
Has the patient been adherent to and tolerated initial therapy?	**Yes**: Approve for additional 12 weeks in genotype 3 patients and genotype 1 patients who are interferon ineligible (refer to dosage and administration table below). If patient is awaiting liver transplantation, approve for up to additional 24 weeks or until liver transplantation, whichever occurs first.	**No:** DENY (Medical Appropriateness)

Dosage and Administration:

Genotype 1 and 4	Sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Genotype 2	Sofosbuvir + ribavirin	12 weeks
Genotype 3*	Sofosbuvir + ribavirin	24 weeks
Genotype 1 and interferon ineligible	Sofosbuvir + ribavirin	24 weeks
Those with hepatocellular carcinoma awaiting liver transplantation	Sofosbuvir + ribavirin	Up to 48 weeks or until ilver transplantation, whichever occurs first

*Certain patients with genotype 3 (nonresponders with advanced fibrosis) can also be treated with sofosbuvir + peginterferon alfa + ribavirin for 12 weeks if deemed appropriate by physician

Hepatitis C Oral Protease Inhibitors/Triple Therapy

Goal(s) :

- Approve treatments of chronic hepatitis C which are supported by the medical literature

Length of Authorization

- Initial trial of 8-12weeks (depending on regimen)
- Continuation of therapy up to 48 weeks of total therapy

Requires PA:

- Telaprevir
- Boceprevir
- Simeprevir

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #3	**No:** Pass to RPh, Deny For Appropriateness
3. Is the prescription for simeprevir?	**Yes: Go to #4**	**No: Go to #6**
4. Has the patient been screened for the presence of virus with the NS3 Q80K polymorphism at baseline?	**Yes: Go to #5**	**No:** Pass to RPh, Deny For Appropriateness. Recommend that the screening take place.
5. Does the patient have the genotype 1 Q80K polymorphism virus?	**Yes:** Pass to RPh, Deny for Appropriateness	**No:** Go To #6
6. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Go to #7	**No:** Pass to RPh, Deny For Appropriateness
7. Is the request for continuation of therapy? (Patient has been on triple therapy with an oral antiviral agent in preceding 6 weeks)	**Yes**: Go to "Continuation of Therapy	**No**: Go to #8
8. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #9	**No:** Pass to RPh, Deny For Appropriateness
9. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #10	**No:** Pass to RPh, Deny For Appropriateness
10. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?	**Yes:** Go to #11	**No:** Pass to RPh, Deny For Appropriateness

11. Does the patient have a biopsy to indicate moderate to severe fibrosis (Metavir score of 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins)?.	**Yes:** Go to #12	**No:** Pass to RPh, Deny For Appropriateness
12. Does the patient have a HIV coinfection?	**Yes:** Go to #13	**No:** Go to #14
13. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #14	**No:** Pass to RPh; Deny (medical appropriateness)
14. Has the patient previously been treated with boceprevir, telaprevir, or simeprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #15
15. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 8 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #16 (If dose is different pass to RPh for appropriateness)
16. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 12 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Go to #17 (If dose is different pass to RPh for appropriateness)
17. Is the request for simeprevir 150 mg once daily for 12 weeks?	**Yes: Approve for 8 weeks to allow for 4 weeks viral load check to continue for a maximum of 12 weeks**	**No: Pass to RPh; Deny for appropriateness**

Continuation of Therapy- Telaprevir		
1. Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
2. Is the patient treatment-naïve or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.

3. Is the patient a prior partial or null responder?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness)
4. Is the patient treatment-naïve with documented cirrhosis that has undetectable HCV-RNA at weeks 4 and 12?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
***TREATMENT FUTILITY RULES** Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks) Week 24: Detectable Discontinue peginterferon and ribavirin. If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued		

Continuation of Therapy- Boceprevir

1. Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (Medical Appropriateness)

2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
3. Is the patient a previous partial responder or relapser and has undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
4. Is the patient a previous partial responder or relapser and has detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
5. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8, 12, and 24?	**Yes:** Approve as follows: • Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).	**No:** DENY (Medical Appropriateness)
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.		

Continuation of Therapy- Simeprevir: Simeprevir in combination with peginterferon alfa and ribavirin should only be given for 12 weeks. No more simeprevir should be approved. The following are the recommended duration of treatments for dual therapy with peginterferon alfa and ribavirin after the initial 12 weeks of triple therapy

1. Is the patient treatment-naïve or a prior relapse and has undetectable HCV RNA (< 25 IU/ml) at week 4?	**Yes:** Approve as follows: • Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients.
2. Is the patient a prior non-responder (including partial and null responders) and has an undetectable HCV RNA (<25 IU/ml) at week 4?	**Yes:** Approve as follows: • Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 25 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue two-medicine regimen.		

Interferons and Ribavirins

Goal(s):

Cover drugs only for those clients where there is medical evidence of effectiveness and safety

Length of Authorization: 16 weeks plus 12-36 additional weeks or 12 months

Requires pa: All drugs in HIC3 = W5G

Preferred Alternatives: See PDL list at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Is peginterferon requested preferred?	**Yes:** Go to #4	**No:** Go to #2.
2. Will the prescriber consider a change to a preferred product? Message: - Preferred products are evidence-based reviewed for comparative effectiveness & safety Oregon Pharmacy and Therapeutics (P&T) Committee	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	**No:** Go to #3.
3. If the request is for interferon alfacon-1, does the patient have a documented trial of a pegylated interferon?	**Yes:** Go to #4.	**No:** Deny; Pass to RPH (Medical Appropriateness)
4. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code: (571.40; 571.41; 571.49)	**Yes:** Go to #5.	**No:** Go to #11
5. Is the request for continuation of therapy? (Patient has been on HCV treatment in the preceding 12 weeks according to the Rx profile)	**Yes:** Go to "Continuation of Therapy"	. **No:** Go to #6
6. Does the patient have a history of treatment with previous pegylated interferon-ribavirin combination treatment? Verify by reviewing member's Rx profile for PEG-Intron or Pegasys, PLUS ribavirin history. Does not include prior treatment with interferon monotherapy or non-pegylated interferon.	**Yes:** Forward to DMAP Medical Director	**No:** Go to #7
7. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy? • severe or uncontrolled psychiatric disorder • decompensated cirrhosis or hepatic encephalopathy • hemoglobinopathy • untreated hyperthyroidism • severe renal impairment or transplant • autoimmune disease	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #8

• pregnancy • unstable CVD		
8. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?	**Yes:** Go to #9	**No:** Deny; Pass to RPH (Medical Appropriateness)
9. Does the patient have a detectable HCV RNA (viral load) > 50IU/mL? Record HCV RNA and date:	**Yes:** Go to #10	**No:** Deny; Pass to RPH (Medical Appropriateness)
10. Does the patient have a documented HCV Genotype? Record Genotype:	**Yes:** Approve for 16 weeks with the following response: Your request for has been approved for an initial 16 weeks. Subsequent approval is dependent on documentation of response via a repeat viral load demonstrating undetectable or 2-log reduction in HCV viral load. Please order a repeat viral load after 12 weeks submit lab results and relevant medical records with a new PA request for continuation therapy. Note: For ribavirin approve the generic only	**No:** Deny; Pass to RPH (Medical Appropriateness)
11. Is the request for Pegasys and the treatment of confirmed, compensated Chronic Hepatitis B?	**Yes:** Go to #11	**No:** Deny; Pass to RPH (Medical Appropriateness)
12. Is the patient currently on LAMIVUDINE (EPIVIR HBV), ADEFOVIR (HEPSERA), ENTECAVIR (BARACLUDE), TELBIVUDINE (TYZEKA) and the request is for combination Pegasys-oral agent therapy?	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #12
13. Has the member received previous treatment with pegylated interferon?	**Yes:** Deny; Pass to RPH (Medical Appropriateness) Recommend: LAMIVUDINE (EPIVIR HBV) ADEFOVIR (HEPSERA)	**No:** Approve Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime).

Continuation of Therapy- HCV

<table>
<tr>
<td>1. Does the client have undetectable HCV RNA or at least a 2-log reduction (+/- one standard deviation) in HCV RNA measured at 12 weeks?</td>
<td>Yes: Approve as follows:

Approval for beyond quantity and duration limits requires approval from the medical director.

<table>
<tr><th>Genotype</th><th>Approve for</th><th>Apply</th></tr>
<tr><td>1 or 4</td><td>An additional 36 weeks or for up to a total of 48 weeks of therapy (whichever is the lesser of the two).</td><td>Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose =1200 mg).</td></tr>
<tr><td>2 or 3</td><td>An additional 12 weeks or for up to a total of 24 weeks of therapy (whichever is the lesser of the two).</td><td>Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg).</td></tr>
<tr><td>For all genotypes and HIV co-infection</td><td>An additional 36 weeks or for up to a total of 48 weeks of therapy (whichever is the lesser of the two)</td><td>Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).</td></tr>
</table>
</td>
<td>No: DENY
(Medical Appropriateness)

Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.</td>
</tr>
</table>

Clinical Notes:

- Serum transaminases: Up to 40 percent of clients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions.
- RNA: Most clients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 (10^5) and 10,000,000 (10^7) copies per ml. Expressed as IU, these averages are 50,000 to 5 million IU. Rates of response to a course of peginterferon-ribavirin are higher in clients with low levels of HCV RNA. There are several definitions of a “low level” of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per ml.(5)
- Liver biopsy: Not necessary for diagnosis but helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage and for ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.
-

Stage is indicative of fibrosis:			**Grade is indicative of necrosis:**	
Stage 0	No fibrosis			
Stage 1	Enlargement of the portal areas by fibrosis		Stage 1	None
Stage 2	Fibrosis extending out from the portal areas with rare bridges between portal areas		Stage 2	Mild
Stage 3	Fibrosis that link up portal and central areas of the liver		Stage 3	Moderate
Stage 4	Cirrhosis		Stage 4	Marked

The following are considered investigational and/or do not meet medical necessity criteria:

- ✓ Treatment of HBV or HCV in clinically decompensated cirrhosis
- ✓ Treatment of HCV or HBV in liver transplant recipients
- ✓ Treatment of HCV or HBV > 48 weeks
- ✓ Treatment of advanced renal cell carcinoma
- ✓ Treatment of thrombocytopenia
- ✓ Treatment of human papilloma virus
- ✓ Treatment of multiple myeloma

Appendix 2: Abstracts of potentially relevant RCTs

1. Zeuzem et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014 Feb;146(2):430-441.e6.

Background & Aims: Simeprevir (TMC435) is an oral NS3/4 protease inhibitor in phase III trials for chronic hepatitis C virus (HCV) infection. We performed a phase IIb, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the combination of simeprevir, peginterferon-α2a (PegIFN), and ribavirin (RBV) in patients with HCV genotype-1 infection previously treated with PegIFN and RBV.

Methods: We analyzed data from patients who did not respond (null response), had a partial response, or relapsed after treatment with PegIFN and RBV, randomly assigned to receive simeprevir (100 or 150 mg, once daily) for 12, 24, or 48 weeks plus PegIFN and RBV for 48 weeks (n = 396), or placebo plus PegIFN and RBV for 48 weeks (n = 66). All patients were followed for 24 weeks after planned end of treatment; the primary end point was the proportion of patients with sustained virologic response (SVR; undetectable HCV RNA) at that time point.

Results: Overall, rates of SVR at 24 weeks were significantly higher in the groups given simeprevir than those given placebo (61%−80% vs 23%; *P* < .001), regardless of prior response to PegIFN and RBV (simeprevir vs placebo: prior null response, 38%−59% vs 19%; prior partial response, 48%−86% vs 9%; prior relapse, 77%−89% vs 37%). All groups had comparable numbers of adverse events; these led to discontinuation of simeprevir or placebo and/or PegIFN and RBV in 8.8% of patients given simeprevir and 4.5% of those given placebo.

Conclusions: In treatment-experienced patients, 12, 24, or 48 weeks simeprevir (100 mg or 150 mg once daily) in combination with 48 weeks PegIFN and RBV significantly increased rates of SVR at 24 weeks compared with patients given placebo, PegIFN, and RBV and was generally well tolerated

2. Liu CH et al. Pegylated interferon-α2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. Ann Intern Med. 2013 Dec 3;159(11):729-38

BACKGROUND: Data are limited on the efficacy and safety of pegylated interferon plus ribavirin for patients with hepatitis C virus genotype 1 (HCV-1) receiving hemodialysis.

OBJECTIVE: To compare the efficacy and safety of combination therapy with pegylated interferon plus low-dose ribavirin and pegylated interferon monotherapy for treatment-naive patients with HCV-1 receiving hemodialysis.

DESIGN: Open-label, randomized, controlled trial. (ClinicalTrials.gov: NCT00491244).

RESULTS: Compared with monotherapy, combination therapy had a greater sustained virologic response rate (64% vs. 33%; relative risk, 1.92 [95% CI, 1.41 to 2.62]; P < 0.001). More patients receiving combination therapy had hemoglobin levels less than 8.5 g/dL than those receiving monotherapy (72% vs. 6%; risk difference, 66% [CI, 56% to 76%]; P < 0.001). Patients receiving combination therapy required a higher dosage (mean, 13 946 IU per week [SD, 6449] vs. 5833 IU per week [SD, 1169]; P = 0.006) and longer duration (mean, 29 weeks [SD, 9] vs. 18 weeks [SD, 7]; P = 0.004) of epoetin-β than patients receiving monotherapy. The adverse event-related withdrawal rates were 7% in the combination therapy group and 4% in the monotherapy group (risk difference, 3% [CI, -3% to 9%]).

CONCLUSION: In treatment-naive patients with HCV-1 receiving hemodialysis, combination therapy with pegylated interferon plus low-dose ribavirin achieved a greater sustained virologic response rate than pegylated interferon monotherapy.

3. Rodriguez-Torres, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. J Hepatol. 2013 Apr;58(4):663-8. Epub 2012 Nov 23.

BACKGROUND & AIMS: Sofosbuvir (formerly GS-7977) is a pyrimidine nucleotide analog inhibitor of the hepatitis C virus (HCV) NS5B polymerase. We assessed the safety, tolerability, antiviral activity, and pharmacokinetics of sofosbuvir plus pegylated-interferon (PegIFN)/ribavirin (RBV) in a 28-day, dose-ranging trial in treatment-naïve patients infected with genotype 1 HCV.

METHODS: In this double-blind study, 64 patients were randomized (1:1:1:1) to receive one of three once-daily doses of oral sofosbuvir (100, 200, or 400mg) or placebo plus PegIFN/RBV for 28 days, after which all patients continued to receive PegIFN/RBV alone for a further 44 weeks.

RESULTS: Patients in the sofosbuvir/PegIFN/RBV groups experienced mean reductions in HCV RNA >5 $\log_{10}$ IU/ml (-5.3 for 100 mg, -5.1 for 200 mg and -5.3 for 400 mg) vs. -2.8 $\log_{10}$ IU/ml for placebo/PegIFN/RBV after 28 days. Rapid virologic response (RVR) rates were markedly higher after sofosbuvir treatment (88-94%) than placebo (21%), as were rates of sustained virologic response (SVR) at post-treatment Week 24 (56%, 83%, and 80% for sofosbuvir 100, 200, and 400 mg, respectively, vs. 43% for placebo). The number of patients experiencing virologic breakthrough and post-treatment relapse was higher in the sofosbuvir 100 mg group than sofosbuvir 200 and 400 mg groups. Sofosbuvir was well tolerated; the most frequent adverse events were fatigue and nausea.

CONCLUSIONS: These results support further studies with sofosbuvir at 200 mg and 400 mg to determine the optimal dose and treatment duration of sofosbuvir in HCV genotype 1

4. Benhamou et al. Telaprevir activity in treatment-naive patients infected hepatitis C virus genotype 4: a randomized trial. J Infect Dis. 2013 Sep;208(6):1000-7. Epub 2013 Jun 24.

BACKGROUND: This partially blinded, randomized, pha**se 2a C210 study evaluated the antiviral activity of telaprevir-based regimens in treatment-naive** patients with chronic hepatitis C virus (HCV) genotype 4 infection.

METHODS: Twenty-four patients received telaprevir 750 mg every 8 hours for 15 days (T; n = 8), telaprevir in combination with pegylated interferon alfa-2a and ribavirin (Peg-IFN/RBV) for 15 days (TPR; n = 8), or Peg-IFN/RBV plus placebo for 15 days (PR; n = 8), followed by Peg-IFN/RBV for 46 or 48 weeks. The primary objective was to assess the effect of telaprevir on HCV RNA levels.

RESULTS: HCV RNA levels decreased slightly with T and PR; TPR produced substantial, rapid declines. On day 15, median reductions in the HCV RNA load from baseline were -0.77, -4.32, and -1.58 log10 IU/mL for T, TPR, and PR, respectively, and 0 patients in the T group, 1 in the TPR group, and 0 in the PR group had undetectable HCV RNA. Five of 8 patients who received telaprevir monotherapy had viral breakthrough within 15 days of treatment. Adverse event incidence was similar across treatments and comparable with the incidences from previous clinical trials. One patient (in T group) had a serious adverse event (considered unrelated to telaprevir) that led to treatment discontinuation.

CONCLUSIONS: Telaprevir with Peg-IFN/RBV had greater activity than Peg-IFN/RBV treatment or telaprevir monotherapy against HCV genotype 4. Telaprevir was generally safe and well tolerated. Further investigation of telaprevir combination therapy in patients with HCV genotype 4 infection is warranted**.**

Sofosbuvir for the Treatment of Hepatitis C and Evaluation of the 2014 American Association for the Study of Liver Diseases Treatment Guidelines

May 2014

Center for Evidence-based Policy

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About the Center for Evidence-based Policy

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring diverse and relevant perspectives are considered, and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

Suggested citation:

Leof, A., Gerrity, M., Thielke, A., & King, V. (2014). *Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 American Association for the Study of Liver Diseases treatment guidelines.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

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List of Tables and Appendices

Introduction

Chronic Hepatitis C virus (HCV) infection is a slowly progressive condition affecting between 2.7 million and 5.2 million United States (US) citizens (Chak 2011; Denniston 2014). Hepatitis C infection is associated with an increased risk of cirrhosis, liver failure, and hepatocellular carcinoma, and is the most common condition leading to liver transplant. Over a 20- to 30-year period, 5% to 20% of infected patients will develop cirrhosis and 1% to 5% will die of cirrhosis or liver cancer (Center for Disease Control and Prevention [CDC] 2010).

For HCV infected patients who develop liver disease, the most recently recommended standard of care is a combination of pegylated interferon therapy (PEG) and ribavirin (RBV), and, for patients with genotype 1 HCV infection, one of the protease inhibitors boceprevir (Victrelis™) or telaprevir (Incivek™). The standard interferon-based treatment regimens result in 45% to 75% of patients having no detectable virus at 24 weeks post treatment with results varying based on patient characteristics (US Department of Veterans Affairs 2013). These regimens can take up to a year to complete, place a high burden on patients requiring weekly injections and complicated dosing schedules, and are associated with significant side effects leading patients to discontinue treatment. The ideal treatment for HCV would be highly effective, easy to take, have a low side effect profile, have a low patient burden, and be affordable.

Pharmaceutical companies have invested significant resources in finding alternative treatment regimens that would improve rates of sustained viral response while reducing patient burden for patients infected with HCV. More than 30 direct-acting anti-viral agents (DAAs) designed to treat HCV have entered clinical trials since 2011 (Tice 2014). In 2013, two new DAAs were approved: sofosbuvir (Sovaldi™) and simeprevir (Olysio™). At least two more DAAs are expected to be approved in 2014, including faldaprevir and daclatasvir. Gilead is also seeking approval for multi-drug combination pills including sofosbuvir and AbbVie recently reported positive results from its investigational oral regimen (AbbVie 2014).

Of the recently developed DAAs, sofosbuvir has drawn the most attention because it is the first new DAA the US Food and Drug Administration (FDA) approved for the treatment of HCV genotypes 1 to 4 (including an interferon free regimen for genotypes 2 and 3). In addition, many reports of the initial sofosbuvir trials suggest that 80% to 90% of patients will not have detectable virus 12 weeks after completing treatment. In January 2014, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) released treatment guidance for hepatitis C and recommended sofosbuvir for all patients except those with severe renal impairment.

With the recent FDA approval of sofosbuvir, clinicians and purchasers will need to decide whether to include sofosbuvir in their treatment protocols for HCV infection. This report

evaluates the evidence about the effectiveness and harms of sofosbuvir treatment for HCV, evaluates the AASLD guideline, and provides a compilation of the evidence to guide decisions on who and when to treat. With the approval of new HCV treatments and more drug approval applications currently at the FDA, it is clear that this is a rapidly evolving clinical and policy topic. Center for Evidence-based Policy staff will continue to place updated material on the Medicaid Evidence-based Decisions (MED) Project Clearinghouse website and will consider this report for updating as new evidence emerges.

Background

Clinical Overview

Between 2.7 million and 5.2 million Americans are infected with the HCV virus (Chak 2011; Denniston 2014). Prevalence of the HCV infection is greater in Medicaid and non-insured populations than in commercially insured groups, with one Florida study showing the Medicaid infection rate to be twice that of the commercially insured populations (663 per 100,000 beneficiaries compared to 302 per 100,000 over ten years) (Levin 2012). Because the early stages of the disease are often asymptomatic, up to half of infected individuals are unaware of their status. In June 2013, the United States Preventive Services Task Force (USPSTF) recommended that individuals at high risk of infection (intravenous drug users, individuals who received blood transfusions before 1992) and all adults born between 1945 and 1965 be screened for HCV (USPSTF 2013).

Progression of HCV is generally slow and varies significantly by individual. Approximately 15% to 25% of people infected with HCV will clear the virus during the acute stage without treatment. Seventy-five to 85% of infected individuals will develop a chronic HCV infection, and 60% to 70% of patients with chronic infection will develop chronic liver disease. Over 20 to 30 years, 5% to 20% of infected patients will develop cirrhosis and 1% to 5% will die of cirrhosis or liver cancer (CDC 2010).

Table 1. Progression of Hepatitis C Virus Infection (CDC 2014)

Condition	Percentage of Patients Who Develop Condition
Chronic HCV infection	75% to 85%
Chronic liver disease	60% to 70%
Cirrhosis over 20 to 30 years	5% to 20%
Death from cirrhosis or liver cancer	1% to 5%

Accelerated progression of the disease is associated with male gender, greater age, duration of the disease, steatosis, obesity, human immunodeficiency virus infection (HIV), hepatitis B infection (HBV), immunosupression following solid organ transplant, insulin resistance and type

2 diabetes, and significant alcohol consumption (European Association for the Study of the Liver [EASL] 2013; Ghany 2009; Louie 2012). It is also important to note that neither spontaneous clearance nor successful treatment confers immunity and that reinfection can occur (Grebely 2012).

Common comorbid conditions with HCV infection include metabolic syndrome (approximately 27% of infected people), dyslipidemia (16% to 21%), peripheral vascular disease (19%), HIV (4%), and diabetes (5% to 15%) (Levin 2012). In a commercially insured population, alcohol and drug abuse were more common in HCV-infected patients than non-infected controls, with 7% versus less than 1% having an alcohol problem and 15% versus 3% abusing illegal drugs (Louie 2012).

There are six major genotypes of the HCV virus. Genotype 1 (HCV-1) is the most common form found in the US population accounting for approximately 73% of cases. Genotype 1 is further distinguished by subtypes 1a (HCV-1a) (39% of patients) and 1b (HCV-1b) (29%). Genotype 2 (HCV-2) is found in approximately 14% of US patients, genotype 3 (HCV-3) in 8%, a mixed-genotype in 4%, and genotypes 4 through 6 (HCV-4, -5, -6) in less than 1% of patients (Blatt 2000). Patients with genotype 1 have had a poorer response to treatment than patients with genotype 2 or 3, and subtype 1a has a poorer response than subtype 1b.

In addition, people have a gene that is related to Hepatitis C virus infection called the IL28B gene. The IL28B genotype can be of CC, CT or TT type. Patients with IL28B genotype CC are significantly more likely to clear the virus spontaneously and to respond to HCV treatment than patients with types CT or TT (EASL 2013).

Treatment

The goal of HCV treatment is to decrease the risk of virus-related conditions such as cirrhosis, hepatocellular carcinoma (HCC), decompensated liver disease, liver transplant, or death from other liver-related causes. Because of the slow progression of the disease, clinical trials have not evaluated these patient-important conditions as trial outcomes. Instead, a surrogate endpoint of sustained virologic response (SVR) has been used to measure success of treatment. The SVR is defined as undetectable HCV-ribonucleic acid (RNA) levels. The standard measure of treatment success has been SVR at 24 weeks post treatment (SVR24).

Several long term studies of patients with chronic HCV infection have shown an association between achieving SVR24 and patient-important clinical outcomes. In a systematic review by the Agency for Healthcare Research and Quality (AHRQ), Chou (2012) found a moderate strength of evidence that achievement of SVR24 post treatment was associated with lower risks of all-cause mortality, liver-related mortality, and HCC with hazard ratios ranging from 0.10 to 0.71. Chou (2012) also reviewed nine poor-quality studies that found a low strength of evidence

that achieving SVR24 was associated with improvement in generic and disease-specific quality of life. Two additional studies were published since the AHRQ systematic review and corroborate its findings. Van der Meer (2012) found that among patients with HCV and advanced fibrosis or cirrhosis (Ishak scores between four and six) achievement of SVR24 was significantly associated with reduced mortality. The ten-year cumulative all-cause mortality rate in the 192 patients who achieved SVR24 was 8.9% (95% CI, 3.3% to 14.5%) compared to 26% (95% CI, 20.2% to 28.4%) ($p<0.001$) in the 338 patients who failed to achieve SVR24. A 2014 observational study of a VA population found that out of 128,769 patients infected with HCV, the 5180 patients (4%) who were able to achieve an undetectable viral load with interferon-based treatment had a 45% reduction in the risk of death (hazard ratio [HR] 0.55, 95% CI 0.47 to 0.64) and a 27% reduction in the composite clinical endpoint (HR 0.73, 95% CI 0.66 to 0.82) of newly diagnosed cirrhosis, HCC, or a liver-related hospitalization (McCombs 2014).

The FDA recently accepted SVR at 12 weeks post treatment (SVR12) as an endpoint for FDA drug approval (FDA 2013a). This decision is based on a 2013 analysis of data from 13,599 adults (11,730 with genotype 1) treated with double (PEG+RBV) or triple therapy (PEG+RBV+PI) in phase II or III drug development trials. The analysis found an association between SVR12 and SVR24 as measured by a positive predictive value (PPV) of 98%. (Chen 2013). However, there is uncertainty about this result due to uncertainty about how the authors accounted for missing data. Although the authors state that they imputed missing data for some analyses, the data used to calculate their main measure of concordance (positive and negative predictive values) did not employ imputed values. The authors state that "missing viral load data were not used in calculating the tabularized relations between SVR24 and SVR12 or SVR4." There were 1,536 patients excluded with missing data. Ten-thousand one hundred-ninety-four (10,194/11,730 or 87%) genotype 1 patients were included in the analysis. If the 1,536 missing patients were added back into the calculations for PPV making assumptions about the best case scenario (all patients with missing data achieved SVR24) and worst case scenario (all patients with missing data did not achieve SVR24), the range of potential values for the PPV is 77% to 99%., meaning that of a hundred patients, between one and 23 patients who achieved SVR12 will not achieve SVR24. In addition, these calculations are based on trial populations who generally have favorable treatment characteristics and may not reflect patient populations likely to be treated under Medicaid programs.

In contrast to Chen's findings (2013), Thorlund (2014) performed a meta-analysis of randomized controlled trials that treated HCV genotype 1 patients with PEG and RBV. Thorlund found that SVR12 was 5% to 6% higher than SVR24 in these studies (2014). It may be that the association between SVR12 and SVR24 could vary depending on treatment regimen and concordance measures for one treatment cannot be extrapolated from data gathered from other regimens

(Thorlund 2014). If this is true, the lack of data on both SVR12 and SVR24 for the new DAAs precludes certainty about long term effectiveness of these drugs.

The sofosbuvir trial protocols registered in the ClinicalTrials.gov database include SVR24 as a secondary outcome, yet only two of these studies, ELECTRON (Gane 2013) and the NIH-funded study (Osinusi 2013), reported SVR24 data. Thorlund (2014) has called upon researchers in clinical trials to report both SVR12 and SVR24 "to allow for complete transparency and clarity in […] interpretation" (p. 49).

Standard Treatment Regimens

Since the early 2000s, standard treatment for HCV infection has been a combination of pegylated interferon (PEG-INF) in a weekly injection (either PEG-INF alfa-2a or alfa-2b) and ribavirin (RBV) daily (double therapy). In 2011, the FDA approved the protease inhibitors boceprevir (BOC) or telaprevir (TVR) in addition to PEG-INF and RBV to treat genotype 1 (triple therapy). Standard treatment protocols by genotype and the estimated SVR24 rates from treatment are described in Table 2 below.

Table 2. Standard of Care Treatment Regimens (US Department of Veterans Affairs 2013)

Genotype	Treatment	Approximate SVR24 Rate
HCV-1	Double therapy PEG-IFN alfa-2a or alfa-2b weekly + RBV daily for up to 48 weeks	45%
	Triple therapy PEG-INF alfa-2a OR alfa-2b weekly + RBV daily for up to 48 weeks depending on treatment response and either BOC or TVR. BOC is added during weeks 8 to 32 depending on treatment response and TVR is given with PEG-INF and RBV during first 12 weeks of treatment.	65% to 70%
HCV-2	PEG-INF weekly + RBV daily for up to 24 weeks	75%
HCV-3	PEG-INF weekly + RBV daily for up to 24 weeks	75%

Treatment effectiveness for HCV with double or triple therapy varies based on patient characteristics. Patients with genotype 1 are significantly less likely to achieve SVR24 than patients with genotypes 2 or 3. Patients with high pre-treatment viral loads (HCV-RNA greater than 600,000 IU/mL) are also less likely to achieve SVR. Other factors associated with lower response to treatment include male sex, older age, being African American, obesity, diabetes, reduced alanine aminotransferase (ALT) levels, bridging fibrosis or cirrhosis, and a CT or TT polymorphism on the IL28B gene. In patients with genotype 1 treated with PEG-INF and RBV,

SVR24 rates ranged from 69% in patients with the CC genotype, to 33% with CT, and 27% with TT (Ghany 2011). Differences in response rates by race may be related to African Americans being less likely to have the favorable CC polymorphism on the IL28B gene (Chou 2012; Ghany 2011).

Issues with Standard Treatment

Interferon-based treatments have high rates of side effects that affect quality of life. Patients report significant fatigue, headache and flu-like symptoms as well as neuropsychiatric symptoms such as depression. The Veteran's Administration reports that approximately 10% of patients discontinue interferon-based treatment due to side effects (VA 2013). Interferon and RBV are also associated with anemia, neutropenia, thrombocytopenia, ophthalmologic disorders, thyroid dysfunction, and sarcoidosis.

Triple therapy with BOC or TVR involves a high burden on patients as the dosing schedule is complicated with multiple doses during the day and all medication must be consumed with fat. There are also significant drug-drug interactions with BOC and TVR (Ghany 2011). Adverse events associated with these drugs include increased hematological complications (BOC) and increased risk of anemia and severe rash (TVR) that may lead to discontinuation of treatment (Chou 2012).

Deciding to Initiate Treatment

In contrast to conditions where there is rapid progression and an immediate need for treatment (e.g., acute leukemia or serious bacterial infections), hepatitis C is a slowly progressing disease. Fifteen to 25% of infected persons clear the infection spontaneously. For those with ongoing infection, it is a disease where clinicians and patients have the option of delaying or forgoing treatment. Because of the slow progression of the disease as well as the moderate success rates and the side effects of current treatments, many patients have refused interferon-based treatments. Some physicians have also been recommending that patients wait until new treatment regimens are approved by the FDA. Earlier guidelines by the AASLD recommended that patients be monitored and treated if they show signs of liver involvement. Indications include a liver biopsy showing significant fibrosis (bridging or higher), compensated liver disease (defined as total serum bilirubin less than 1.5 g/dL; international normalized ratio [INR] of 1.5; serum albumin greater than 3.4, platelet count of 75,000 mm and no evidence of hepatic decompensation) and acceptable hematological and biochemical indices (hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil court of 1500/mm^3, serum creatinine less than 1.5 mg/dL). Interferon treatment is contraindicated for patients with uncontrolled major depression, solid organ transplant, untreated thyroid disease, severe comorbid health conditions (e.g., hypertension, heart failure, coronary heart disease, diabetes, chronic obstructive pulmonary disease), or known hypersensitivity to medications (Ghany 2009).

Sofosbuvir (Solvadi™)

Sofosbuvir (SOF), manufactured by Gilead Sciences, is a nucleotide analog NS5B polymerase inhibitor. In December 2013, the FDA approved SOF 400mg in a once daily pill for the treatment of hepatitis C genotypes 1, 2, 3 and 4, in combination with RBV and, for genotype 1, PEG-INF. The approval specifically includes patients who have the most urgent need for treatment due to advanced disease and increased risk of death including those with HCC, those awaiting liver transplantation, and patients with HIV-1 co-infection. Sofosbuvir is not approved for patients with severe renal impairment (estimated glomerular filtration rate less than or equal to 30 mL/min/1.73m^2) or end stage renal disease. The FDA approved sofosbuvir under a priority review process that allowed use of SVR12 as a study endpoint. Approved treatment regimens are described in Table 3 below.

Table 3. FDA Approved Sofosbuvir Treatment Regimens (FDA 2013b)

Patient Genotype	Treatment Regimen	Duration[1]
HCV-1 or -4	PEG-INF weekly + RBV + SOF daily	12 weeks
HCV-1	For interferon-ineligible: RBV + SOF	24 weeks
HCV-2	RBV + SOF	12 weeks
HCV-3	RBV + SOF	24 weeks

[1]All medications are taken for the full duration.

The FDA approved label for Sofosbuvir does not identify any adverse reactions besides those that commonly occur with RBV treatment (fatigue and headache) or PEG-INF (fatigue, headache, nausea, insomnia, and anemia).

Sofosbuvir has attracted attention because of its potential improvement over previous standard of care. For genotypes 2 and 3, SOF plus RBV provides an interferon-free, all oral regimen with shorter duration. For genotype 1, SOF provides an alternative to BOC and TVR with their higher pill burden and side effect profile; it provides a shorter treatment period; and, for interferon-ineligible patients, it offers an alternative treatment protocol. Studies report SVR12 rates of 80% to 90% in patients treated with sofosbuvir regimens, and low rates of serious adverse events. If, indeed, the clinical research evidence supports these claims, the new SOF regimens would be a tremendous step forward for patients with HCV.

Gilead Science has set the wholesale acquisition cost of sofosbuvir at $1,000 per tablet in the U.S. With daily dosing, the cost of a course of treatment with sofosbuvir will range from $84,000 for 12 weeks to $168,000 for 24 weeks of treatment (Robison 2013). This price does not include the drug cost of RBV and/or PEG-INF in regimens that include those drugs. These costs also do not account for the medical care needed before, during and after treatment, or further treatment in the case of treatment failure or relapse.

Key Questions

This report will address the following key questions:

1. What is the evidence for the efficacy of sofosbuvir in treating hepatitis C?
2. What is the evidence for harms of sofosbuvir treatment?
3. Is there any evidence of subgroup differences in efficacy and harms (e.g., genotype, race, comorbidity)?
4. Are there studies in the research pipeline that will add significantly to the knowledge of sofosbuvir's effectiveness and harms?
5. What polices have private payers set around sofosbuvir coverage?
6. What is the quality and reliability of the AASLD treatment guideline?
7. What does the evidence say about whom to treat and when to treat?

Methods

Search Strategy

The FDA's website was searched for the summary review of evidence and the approved label for sofosbuvir. The website clinicaltrials.gov was searched with the term "sofosbuvir" and all studies were reviewed for their design, treatment population, interventions and outcomes. Completed studies were reviewed to identify publications. A MEDLINE search was conducted with the search term "sofosbuvir" and all studies examining efficacy and harms of sofosbuvir were included regardless of design. Editorials, letters, and commentaries were excluded. Studies were also initially excluded if they were unpublished or presented in abstracts or slides since details about study design and patient characteristics were not available. However, after peer review comments were received additional studies available in abstract form only and unpublished studies from the information submitted by the manufacturer for FDA review were included. Due to insufficient information within these documents, formal methodological quality assessment was not performed on abstracts or unpublished trials.

The search for relevant clinical practice guidelines included the following sources: UK National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), USPSTF, Institute for Clinical Systems Improvement (ICSI), and Australian Government National Health and Medical Research Council (NHMRC), Veterans Affairs guidelines, and gastroenterology and hepatology professional organizations.

Quality and Applicability Assessment

All identified published studies were included for review. Three reviewers rated the quality (risk of bias or internal validity) of each study as well as criteria to assess the risk for biased inferences from study results (external validity or applicability) due to factors such as inappropriate comparator or outcome for the key questions raised in this report. Several

studies presented in abstracts and slides were later summarized, based on requests from external reviewers, but were not quality rated.

A checklist was adapted from those used by the National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guideline Network (SIGN), Drug Effectiveness Review Project (DERP) for risk of bias (internal validity). Reviewers used a checklist based on criteria proposed by Montori (2004) to address potential biases in inferences made from study results for questions posed in this report (external validity). Finally, conflicts of interest and study funding were noted. Disagreements were resolved by discussion and studies received an overall quality rating that incorporated both risk of bias related to study results and applicability of study results to questions in this report (Appendix D).

Table 4. Critical Appraisal and Summary Judgment

Author, Year (Trial)	How well was the study done to minimize bias in study design? (Good, Fair, Poor)	How well did the study respond to the PICO of this report? (Good, Fair, Poor)	Overall Study Quality (Good Fair, Poor)
Gane, 2013 (ELECTRON)	Poor	Poor	Poor
Jacobson, 2013a (Study 1) (POSITRON)	Poor	Poor	Poor
Jacobson, 2013a (Study 2) (FUSION)	Poor	Poor	Poor
Kowdley, 2013 (ATOMIC)	Poor	Poor	Poor
Lawitz, 2013 (Lancet)	Poor	Poor	Poor
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	Poor	Poor	Poor
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	Poor	Poor	Poor
Osinusi, 2013 (Study 1)	Poor	Poor	Poor
Osinusi, 2013 (Study 2)	Poor	Fair	Poor
Rodriguez-Torres, 2013	Poor	Poor	Poor

Two raters independently rated the quality of the guidelines using a checklist adapted Appraisal of Guidelines Research & Evaluation (AGREE) instrument. Disagreements were resolved by discussion. For guidelines to be considered evidence-based, the following criteria had to be

met: systematic search for studies; study selection criteria clearly described; quality of individual studies and overall strength of evidence assessed; methods for formulating recommendation clearly described; benefits/side effects/risks considered; explicit link between evidence and recommendations; external review; funding source and member conflict of interest managed so as not to influence recommendations.

Peer Review

The draft report was peer reviewed by four experts representing the fields of pharmacology, hepatology, primary care, clinical epidemiology and health policy. Potential reviewers were asked to declare any significant financial or intellectual conflicts of interest. None of the experts who completed the standardized peer review form reported conflicts of interest. A table of de-identified peer reviewer comments along with their disposition was developed and a final version of this report prepared by the authors.

Findings

Seven publications addressing the effectiveness and harms of sofosbuvir (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Osinusi 2013; Rodriguez-Torres 2013) were identified. These seven publications described ten studies, with three articles (Jacobson 2013a, Lawitz 2013b, and Osinusi 2013) describing two studies each. In addition, three studies cited in the FDA review which have not been published were reviewed and data from these trials was included in the appendices where appropriate (Mishra 2013). Three abstracts presented at two conferences on the unpublished COSMOS trial of a sofosbuvir and simeprevir treatment regimen were also reviewed and are described below (Jacobson 2013b; Lawitz 2014; Sulkowski 2014). .

Full study descriptions are offered in Appendix C titled Evidence Table. The evidence table gives detailed information about each study, including design, sample size, inclusion and exclusion criteria, patient characteristics, the drug regimen and comparator employed, the primary outcomes reported and study limitations. In addition, Appendix A presents response and relapse rates by study and Appendix B breaks down study populations by important characteristics (i.e., HCV genotype, prior treatment experience, proportion of male and Caucasian subjects in study, and proportion of subjects with cirrhosis or bridging fibrosis). A table summarizing the findings from the detailed critical appraisal assessment conducted on each of these studies is presented in Appendix D. This report identified 53 studies registered on clinicaltrials.gov, of which 15 were marked as completed. Of the 15 trials marked as completed, only four trials had results posted on clinicaltrials.gov.

The only guideline that addressed the use of sofosbuvir is the 2014 AASLD publication.

Treatment Effectiveness

Overview – Published Studies

Of the ten published studies, there was one placebo controlled trial (Jacobson 2013a, POSITRON) and one study that compared SOF + weight-based RBV to PEG + low dose RBV 3 (Lawitz 2013b, FISSION). Both of these studies included patients with HCV genotypes 2 and 3. All other studies were designed to refine drug dose, drug combination or duration of treatment. Nine studies enrolled patients with HCV-1 (total n=889), five included those with HCV-2 or HCV-3 (total n=1060) and two studies also included patients with HCV-4, -5, or -6 (total n=41).

Studies tended to include populations with favorable prognostic factors. About 10% of total enrolled populations were African or African American. Slightly over 13% had cirrhosis. No subjects with concurrent hepatitis B or HIV infections were included among the published studies. However, one study of HCV/HIV co-infected patients (Mishra 2013, PHOTON-1) was included in the FDA review and available details of the study are described below.

All studies were rated as having a high risk of bias. No study was judged to have good applicability, and only the National Institutes of Health (NIH) sponsored study by Osinusi (2013) was rated as having fair applicability. The overall summary judgment for each of the published studies yielded a rating of poor. Only one of 10 published studies used a comparator that would answer the key clinical question raised in this report – do the new sofosbuvir drug regimens have better clinical outcomes and fewer harms than the current standard of care? In other words, do the sofosbuvir trials compare the current treatment (see Table 2) to the newly recommended sofosbuvir regimens (see Table 3)? These nine published studies, as well as the three unpublished trials included in the FDA review, were single arm non-comparative studies, placebo controlled, or dose or duration varying studies that did not have a meaningful comparator. The outcomes of these studies (e.g., SVR12, SVR24, harms) may be strongly influenced by the characteristics of the patients in the studies, many of whom had characteristics associated with better outcomes (e.g., Caucasian, , lower viral load at baseline, no active or excessive alcohol use, low rates of cirrhosis, other comorbid conditions such as cardiac disease). The one study which did compare the sofosbuvir regimen to the standard PEG and RBV treatment used a low dose of RBV (800mg) rather than weight-based RBV (1000 to 12000 mg depending on weight) which is the current standard of care. Neither this comparator nor the placebo controlled trial were appropriate study designs for answering the questions raised by this report.

No study of sofosbuvir in HCV-1 populations compared the drug to current standard of care, which is triple therapy including PEG-INF + RBV with boceprevir or telaprevir. Most studies were open label and all but one (Osinusi 2013) were funded and controlled by the drug's manufacturer. Most study arms included few patients, especially among subgroups of particular interest to public payers. Duration of follow-up was limited with no study reporting primary

outcomes at more than 24 weeks after the end of treatment. Most studies were multi-centered, and eight studies enrolled 10 or fewer patients per site. None of these studies reported results by study center.

Response rates tended to vary by the underlying prognostic factors of the population (i.e., genotype, presence of cirrhosis, prior treatment status), sample size and study characteristics. Response rates from the published studies, using SVR12 as the outcome measure, ranged from 10% to 89% for patients with HCV-1, 82% to 95% for HCV-2, and 30% to 84% for patients with HCV-3 (Appendix A and B). Few studies reported SVR24, and among the eight study arms reporting both SVR12 and SVR24, the differences in these response rates ranged from 0% to 7%.

Not all studies reported relapse rates and those that did used various measures of "relapse." Relapse is defined as a patient achieving HCV RNA < lower limit of quantitation (LLOQ) or the lower limit of detection (LLOD) at the last measurement on treatment but subsequently having a HCV RNA ≥ LLOQ or LLOD post treatment. The FDA analysis (Mishra 2013) as well as the FISSION, NEUTRINIO, POSITRON, and FUSION studies (Lawitz 2013b; Jacobson 2013a) all defined the LLOQ as < 25 IU/mL. The ELECTRON study (Gane 2013) used a measure of LLOD of < 15 IU/mL while the NIH study (Osinusi) measured both LLOQ and LLOD, but the thresholds varied based on the assay used. Osinusi specified that when using the Abbot Molecular assay, the LLOQ should be < 12 IU/mL and the LLOD < 3 IU/mL, but when using the COBAS TaqMan assay, LLOQ < 43 IU/mL and LLOD < 12 IU/mL. The FDA review (Mishra 2013) did not specify which assay was used to determine LLOQ, but Gane (2013), Jacobson (2013a), and Lawitz (2013) all used the COBAS TaqMan assay.

In those studies that did report relapse rates, some reported only on the basis of per-protocol analysis (patients completing treatment only) and did not account for losses to follow-up. Relapse rates ranged from 5% in treatment naïve genotype 2 patients treated with SOF + RBV for 12 weeks, (FISSION, Lawitz 2013b; POSITRON, Jacobson 2013a) to 90% in treatment experienced genotype 1 patients treated with the interferon-free SOF + RBV 12 week regimen (Gane 2013). For the FDA approved treatment regimens, relapse rates were 4% to 8.6% for genotype 1 patients treated with SOF + PEG + RBV for 12 weeks (Lawitz 2013a; Lawitz 2013b) and 28% for genotype 1 patients treated with the interferon free SOF + RBV for 24 weeks (Osinusi 2013). For genotype 2 patients treated with SOF + RBV for 12 weeks, relapse rates ranged from 5% to 18% (Jacobson 2013a; Lawitz 2013b) and for genotype 3 patients treated with SOF + RBV for 24 weeks, the relapse rates was 14% (Mishra 2013).

Overview – Unpublished Studies Included in FDA Review

Three additional unpublished studies were identified. These three studies, VALENCE, PHOTON-1 and an unnamed trial in pre-transplant patients, were all on-going trials at the time of FDA review but were included in the FDA's efficacy and safety assessment.

The original protocol for VALENCE was as a placebo controlled trial of SOF + RBV for 12 weeks in patients with HCV genotypes 2 or 3. Early results, primarily from the FUSION trial, however, indicated that SVR12 rates in genotype 3 patients improved with longer duration of treatment, and so the protocol for VALENCE was redesigned to treat all genotype 2 patients with SOF + RBV for 12 weeks, and offer genotype 3 patients SOF + RBV for 24 weeks. The SVR12 rate for genotype 3 patients in the trial who took 12 weeks of treatment was 56%, which increased to 93% with 24 weeks of treatment. The relapse rate decreased from 40% to 5%. The VALENCE trial led the FDA to approve a genotype 3 treatment regimen of SOF + RBV for 24 weeks (Mishra 2013).

The PHOTON-1 trial was an on-going, three arm trial of SOF + RBV therapy in patients co-infected with HIV. The first arm included treatment naïve patients with genotype 2 or 3 who received 12 weeks of therapy. The SVR12 rate for the genotype 2 patients was 88% (23/26) and 67% (28/42) for genotype 3. The second arm included treatment experienced patients with genotypes 2 and 3, and they received 24 weeks of treatment. The SVR12 rates were 93% for genotype 2 (14/15) and 92% (12/13) for genotype 3. The third arm included treatment naïve genotype 1 patients who received SOF + RBV for 24 weeks, and the SVR12 response was 76% (87/114). Genotype 1a responded better with 82% achieving SVR12 (74/90) compared to genotype 1b where only 54% (13/24) achieved SVR12 (Mishra 2013).

The FDA also included data from an unnamed, on-going, open-label trial evaluating whether administering SOF + RBV to pre-transplant patients would prevent HCV recurrence post-transplant (trial number P7977-2025). The trial reported incomplete data on a total of 61 patients (Mishra 2013). The preliminary results are presented in Appendix C.

All three of these unpublished trials were incomplete at the time of FDA review and had not been published in a peer reviewed publication as of April 2014. Available details of the trials are included in report charts and tables, but the studies were not quality assessed or reviewed due to lack of information.

Summary of Evidence on FDA Approved Treatment Regimens

Of the 11 studies identified which evaluated sofosbuvir treatment in general populations (ten published studies and the unpublished VALENCE trial, excluding the HIV and pre-transplant studies), only six studies tested one of the four FDA approved treatment regimens. These studies are summarized in Table 5 below.

Table 5. FDA Approved Treatment Regimens and Response Rates

FDA Approved Treatment Regimens and Response Rates					
Genotype	**Treatment**	**SVR12**	**Relapse**	**# of Studies (Study name)**	**Study N**
HCV-1	SOF+PEG+RBV 12 w	89%	4% to 8.6%	2 (NEUTRINO, ATOMIC)	379
	SOF+RBV 24 w	68%	28%	1 (Osinusi, NIH Study)	60
HCV-2	SOF+RBV 12 w	82% to 95%	5% to 18%	4 (FISSION, FUSION, POSITRON, VALENCE)	1051
HCV-3	SOF+RBV 24 w	84%	14%	1 (VALENCE)	250

Note that for both genotype 3 and the interferon-free regimen for genotype 1, the evidence base consists of one study and the total number of patients with reported data is 60 (for genotype 1 patients treated with the interferon-free regimen) and 250 (genotype 3 regimen). The evidence for the genotype 1 SOF + PEG + RBV 12-week treatment is primarily based on the NEUTRINO study which tested the regimen on a total of 327 patients. Fifty-two additional patients also received that treatment regimen in the ATOMIC study that evaluated duration ranges. The genotype 2 regimen has the most documented evidence with the SOF + RBV 12-week treatment being tested on 1051 patients in four trials, and the SVR12 rate varied from 82% to 95%.

Adverse Events

The FDA compiled reports of adverse events from four trials (FISSION, FUSION, NEUTRINO, POSITRON) compiling a data-set of 1305 patients treated with sofosbuvir and RBV, with or without PEG, or placebo. There were no treatment-related deaths reported.

Approximately 78% of patients receiving placebo, 88% of patients on SOF + RBV treatment and 95% of patients receiving PEG + SOF + RBV reported a side effect from treatment. The most common side effects were fatigue, anemia, nausea, rash, headache, insomnia, and pain (Mishra, 2013, p. 115).

Discontinuation of therapy due to adverse events was relatively low in these studies. In the combined safety analysis, the FDA reported withdrawal rates of approximately 1.4% in patients receiving SOF + RBV for 12 weeks (eight out of 566 patients). This compares to 4.2% of patients receiving placebo (three out of 71 patients), 1.5% of patients receiving SOF + PEG + RBV for 12 weeks (five out of 327 patients), and 10.7% of patients on PEG + RBV alone (26 out of 243 patients) (Mishra 2013, p. 109).

Fifty-one treatment-emergent, serious adverse events (SAE) occurred in 34 patients (2.6%). The events by treatment regimen are summarized in Table 6 below.

Table 6. Total Number of Patients with Serious Adverse Events

Regimen	Placebo 12 wks	SOF+RBV 12 wks	SOF+RBV 16 wks	PEG+SOF+RBV 12 wks	PEG+RBV 24 wks
N	71	566	98	327	243
Number of pts w/ SAE	2 (2.8%)	22 (3.9%)	3 (3.1%)	4 (1.2%)	3 (1.2%)
Number of SAEs	3	31	3	8	6
SAES (# of events)	Pancreatitis (1); bile duct stone (1); bronchitis (1);	Anemia (1); abdominal pain (1); non-cardiac chest pain (1); pyrexia (2); chest pain (1); drug withdrawal syndrome (1); edema peripheral (1); portal vein thrombosis (1); allergy to arthropod sting (1); hypersensitivity (1); cellulitis (2); abdominal abscess (1); osteomyelitis chronic (1); urinary tract infection (1); overdose (1); spinal compression fracture (1); fall (1); injury (1);	Non-cardiac chest pain (1); overdose (1); suicide attempt (1);	Anemia (1); leukopenia (1); abdominal pain (1); non-cardiac chest pain (1); pyrexia (1); cryoglobulinaemia (1); spinal compression fracture (1); laryngeal cancer	Atrioventricular block (1); infection (1); clavicle fracture (1); rib fracture (1); breast cancer in situ (1); pneumothrorax (1)

Regimen	Placebo 12 wks	SOF+RBV 12 wks	SOF+RBV 16 wks	PEG+SOF+RBV 12 wks	PEG+RBV 24 wks
		road traffic accident (1); toxicity to various agents (1); upper limb fracture (1); hypoglycemia (1); hepatic neoplasm malignant (3); basal cell carcinoma (1); abnormal behavior (1); COPD (1); eczema (1)			

Adapted from Mishra 2013, p.101.

The other studies reviewed reported similar high rates of mild to moderate side effects such as fatigue, nausea and headache. No significant patterns in serious adverse events were noted.

In assessing the risk of adverse events, it is important to note that the studies on sofosbuvir were small, included populations that were healthier than the general hepatitis C population, were of short duration and had limited follow-up. In many of the studies, the manufacturer was responsible for recording and reporting adverse events. In general, reporting of adverse events is often incomplete and discrepancies between clinical trial reports and publications are common (Hartung 2014). All of these factors would lead to a bias in under-representing the true nature of adverse events.

Long range studies and expanded use may reveal a different harms profile as adverse events associated with new medications often appear only after general clinical use (Prasad 2013). When the protease inhibitors BOC and TVR were approved, studies showed 9% to 14% of patients experienced serious side effects. Post approval studies in Europe found the rate of serious adverse events to be significantly higher, with 38% of patients treated with boceprevir experiencing an adverse event and 48.6% of those receiving telaprevir developing a serious side effect (Hezode 2012).

While the studies reviewed here do not report significant adverse events associated with sofosbuvir treatment, larger and longer term studies would be needed to accurately describe the drug's harms profile.

Subgroup Differences in Effectiveness and Harms

The 11 studies reviewed did not report effectiveness or harms data separately for many relevant subgroups (e.g., by race, gender, IL28B genotype). These studies did suggest that sofosbuvir treatment regimens are similar to interferon-based treatment regimens in that the treatment is more effective in patients with genotype 2 and 3 than in patients with genotype 1, patients with genotype 2 do better than patients with genotype 3, patients with the IL28B CC genotype fare better, and patients without cirrhosis are more likely to achieve SVR12 than those with cirrhosis.

Additional Studies

Due to the rapidly changing environment and information surrounding treatment options for HCV, several peer reviewers suggested including the COSMOS study which tests a treatment regimen of both simeprevir and sofosbuvir for HCV genotype 1 patients. The study remains unpublished.

COSMOS [Sofosbuvir (Sovaldi™) and Simeprevir (Olysio™)]

Simeprevir (Olysio™) is a NS3/4A protease inhibitor jointly developed by Janssen R&D and Medivir AB. In October 2013, the FDA approved simeprevir for the treatment of HCV genotype 1 patients in combination with PEG and RBV.

In November 2013, preliminary results from the COSMOS trial were presented at the annual meeting of the American Association for the Study of Liver Diseases (AASLD). The COSMOS trial includes 167 patients divided into two cohorts each with four study arms and treats these HCV genotype 1 patients with 400 mg SOF and 150 mg SMV with or without weight-based ribavirin for 12 or 24 weeks. The2013 AASLD presentation reported data for the 80 patients in Cohort 1 who were all non-responders to prior treatment with PEG and RBV and who had Metavir fibrosis scores of F0 to F2. The preliminary results were published in *Hepatology* in December 2013 (Jacobson 2013b).

In April of 2014, during the European Association for the Study of the Liver (EASL) conference, two additional presentations on COSMOS trial data were made with the abstracts published on the conference website. The first abstract (Sulkowski 2014) was presented as a “subgroup analysis” of COSMOS, but essentially repackaged the data previously presented at the 2013 AASLD conference which was published in *Hepatology* (Jacobson 2013b). The data is from Cohort 1 (HCV genotype 1 patients with prior non-response to therapy) but the EASL presentation excludes “five patients withdrawn for non-virologic failure” and thus the reported SVR12 rates increase significantly in one treatment group (SMV + SOF + RBV for 24 w, see Table 7 below). The second abstract (Lawitz 2014) reported SVR12 results from Cohort 2 patients who

were either treatment naïve or prior null responders with Metavir scores of F3 to F4. The SVR12 results are summarized in Table 7 below.

Table 7. COSMOS Trial – SVR12 Results

COSMOS SVR12 Results Presented at AASLD and EASL Conferences					
Cohort	**Citation**	**SOF + SMV 12 weeks**	**SOF+SMV+RBV 12 weeks**	**SOF + SMV 24 weeks**	**SOF+SMV+RBV 24 weeks**
1	AASLD 2013 (Jacobson 2013b)	92.9% (13/14)	96.3% (26/27)	100% (14/14)	79.2% (19/24)
	EASL 2014 (Sulkowski 2014)	92.9% (13/14)	96.3% (26/27)	100% (13/13)	90.5% (19/21)
2	EASL 2014 (Lawitz 2014)	92.9% (13/14)	92.6% (25/27)	100% (16/16)	93.3% (28/30)

Adverse events (AEs) occurred in approximately 77% of individuals in both cohorts. For Cohort 1, Jacobson (2013b) reported that four patients (2.4%) discontinued treatment due to AEs while Sulkowski (2014) reported two discontinuations due to AEs. For Cohort 2, Lawitz (2014) reported two discontinuations (2.3%). Jacobson (2013b) reported three serious AEs (1.8%) in Cohort 1; however, Sulkowski (2014) reported no serious AEs. Lawitz (2014) reported four serious AEs but did not provide details.

The abstracts do not present sufficient information to assess adverse events fully or to judge study quality.

No other published studies on the SOF and SMV combination treatment have been identified. In total, there is data on this treatment regimen in 58 genotype 1 patients, 28 of whom had a 12-week course of treatment and 30 who received the drugs for 24 weeks.

Drug Research Pipeline

As of March 7, 2014, there were 53 studies registered on clinicaltrials.gov that include the drug sofosbuvir. The majority of the studies are similar to the studies reviewed in this report in that they compare different doses of sofosbuvir or vary duration of treatment in defined populations. No registered studies compare a sofosbuvir-based regimen with current standard of care (e.g., interferon based double or triple therapy). All but four of the studies are sponsored by sofosbuvir's manufacturer, Gilead Science, and the other trials are sponsored by Bristol Myers (three trials combining sofosbuvir and daclatasvir) and the University of Florida with Vertex Pharmaceuticals (sofosbuvir combined with telaprevir).

Twenty-two of the registered studies test regimens that combine sofosbuvir with other new DAAs. Most significantly, the manufacturer has registered 15 trials of a sofosbuvir/ledipasvir fixed dose combination (FDC) pill with or without ribavirin in all genotypes. These trials do not include interferon. The manufacturer has also registered four trials combining sofosbuvir treatment with unnamed drugs identified as GS-9669, GS-9938, and GS-5816.

Several trials address specific populations, including HIV co-infection (one completed study, not yet published and two studies in progress), patients with renal insufficiency, pre and post-liver transplant, and cirrhosis. No trials examine sofosbuvir, interferon and ribavirin in genotype 1 patients who have previously failed treatment. There are four trials that administer the sofosbuvir/ledipasvir FDC with or without ribavirin to genotype 1 patients who have failed treatment. Those trials are scheduled for completion between July and December 2014.

In summary, there are no studies registered in clinicaltrials.gov which compare sofosbuvir-based treatment to the current standard of care, there is no forthcoming evidence on sofosbuvir, interferon, and ribavirin treatment in genotype 1 patients who have failed previous treatment, and there are no registered studies being conducted by any parties other than pharmaceutical companies.

Private Payer Policies

A review of Center core policy sources and references from the California Technology Assessment Forum draft report (Tice 2014) identified six private payer policies on sofosbuvir: Aetna, Anthem/Express Scripts, Caremark/CVS, Cigna, HealthNet, and Humana. Copies of these policies are included in Appendix E. Four of the policies cover sofosbuvir for all FDA approved indications, although three payers require evidence of compensated liver disease and Humana requires that patients with genotype 1 have previously failed treatment with triple therapy or have documented contraindications to interferon therapy. Cigna has published a prior authorization form but does not have coverage criteria publicly available. The private payer policies are summarized in Table 8 below.

Table 8. Private Payer Policies

Payer	Prior Authorization	Approved for all FDA Indications	Notes
Aetna	Yes	Yes	Allows for simeprevir and sofosbuvir combination treatment for genotype 1 PEG ineligible or non-responder
CareMark	Yes	Yes	Excludes ESRD, decompensated cirrhosis, post liver transplant, or significant or unstable cardiac disease

Payer	Prior Authorization	Approved for all FDA Indications	Notes
Cigna	Yes	Unclear	PA form requests information but does not list approval criteria
Anthem/Express Scripts	Yes	Yes	Requires compensated liver disease including cirrhosis
Health Net	Unclear	Yes	Requires liver biopsy showing fibrosis Metavir score ≥ 2 or Ishak score ≥ 3 Policy states that treatment is not authorized for "treatment regimen that patient who has failed therapy with an NS3/4A protease inhibitor (e.g., boceprevir, simeprevir, telaprevir)." Not authorized for post-liver transplant Explicitly excludes simeprevir and sofosbuvir combination treatment
Humana	Yes	No	Requires compensated liver disease Genotype 1 without HIV or HCC requires prior treatment failure with PI triple therapy Approved for all other FDA indications

Abbreviations: ESRD – end-stage renal disease; HIV – human immunodeficiency virus; HCC – hepatocellular carcinoma; PA – prior authorization; PI – protease inhibitors

Note: Private payer policies state coverage subject to individual member benefit contracts.

Guideline Assessment

The only identified guideline addressing the use of sofosbuvir is published by the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Hepatitis C Guidance (AASLD 2014). The AASLD/IDSA Hepatitis C Guidance was published in January 2014 and includes 27 recommended treatment regimens based on HCV genotype, prior treatment, and co-morbid conditions and nine alternative treatment regimens. All 27 recommended regimens include sofosbuvir except in patients with severe renal impairment.

When the guideline was published, the authors noted that three sections would be "coming soon":

- In whom and when to initiate treatment;
- Monitoring patients who are on or have completed therapy; and

- Management of acute HCV infection.

As of May 1, 2014, the additional sections had not been published. The guideline is available on a dedicated website: http://www.hcvguidelines.org.

The overall methodologic quality of the guidance was poor (see Table 9 below). Two areas raised the greatest concern. First, there were no assessments of risk of bias (quality) for individual studies or the overall strength of the evidence cited for each recommendation. The published studies cited in the AASLD/IDSA Guidance as supporting the efficacy of sofosbuvir are described in other sections of this report. As noted above, all of the 10 published studies (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Rodriguez-Torres 2013; Osinusi 2013) were given a poor quality summary rating. Second, there is substantial risk of conflict of interest influencing the recommendations from both individual panel members and funding source. For example, four of the five panel chairs had financial relationships with Gilead Science, as did 15 of the 21 panel members. Although members were given the "opportunity" to divest and recuse themselves from discussions or be recused by the chair, there was no description of when or how this occurred. More important, the International Antiviral Society-USA (IAS-USA) was the collaborating partner for development of the guidance. It was "responsible for providing expertise and managing the [p]anel and the [g]uidance development process", and one of the five panel chairs was from this society. Funding for the IAS-USA is primarily from the pharmaceutical industry including Gilead Science.

Table 9. AASLD/IDSA Hepatitis C Guidance Quality Assessment*

Category	Rating
Primary Criteria	
Rigor of development: Evidence	Poor
Rigor of development: Recommendations	Poor
Editorial independence	Poor
Secondary Criteria	
Scope and purpose	Fair
Stakeholder involvement	Fair
Clarity and presentation	Fair
Applicability	Poor
Overall rating	**Poor**

*Checklist adapted Appraisal of Guidelines Research & Evaluation (AGREE) instrument. Each category rated as good, fair or poor by two raters who were consistent in all ratings. To be considered evidence-based, none of the primary criteria should receive a poor rating.

In summary, the ASSLD/IDSA Guidance was found to be of poor methodological quality as its findings were based on poor quality evidence and the authors and sponsors of the guidance had multiple and significant conflicts of interest.

Who to Treat and When to Treat

The primary goal of treating patients with chronic HCV infection is to prevent long-term complications including cirrhosis (compensated and decompensated), HCC, and mortality. Hepatitis C is a slowly progressive disease and current treatments have significant side effects making it difficult to determine who to treat and when (Davis 2010). The AASLD and others suggest using the following guiding principle in selecting patients for treatment – *antiviral treatment should be considered in patients who are at greatest risk of progressing to cirrhosis or serious hepatic complications from HCV (e.g., decompensated cirrhosis, HCC, death) or extra hepatic complications such as cryoglobunimia* (AASLD 2009; SIGN 2013; Veterans Health Administration Pharmacy Benefits Management 2014). Ongoing trials involving new direct acting agents may clarify treatment choices in the next one to two years.

In general, patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis as defined by Metavir fibrosis stage 2 or greater (portal fibrosis with few septa – see Table 10 below). In fact, the current AASLD-IDSA Guidance (AASLD 2014) states that "it may be advisable to delay treatment for some patients with documented early fibrosis state (F 0 to 2), because waiting for future highly effective, pangenotypic, DAA combinations in INF-free regimens may be prudent" (p.31). Other risk factors for progression are listed in Table 11 and mirror the factors predicting response to treatment (Table 12) (AASLD 2009; Chou 2012; Freeman 2001; Thein 2008; Yee 2012). These factors may play an additional role in identifying patients most likely to benefit from treatment. Patients with compensated cirrhosis (total serum bilirubin less than 1.5 g/dL, INR less than or equal to 1.5, serum albumin greater than 3.4 g/dL, platelet count greater than or equal to 75,000/mm^2, no evidence of ascites or hepatic encephalopathy) are at risk of progressing to decompensation, HCC, or death.

Table 10. Metavir Fibrosis Scores

Score	Description
F0	No fibrosis
F1	Portal fibrosis without septa
F2	Portal fibrosis with few septa
F3	Numerous septa without cirrhosis
F4	Cirrhosis

Table 11. Risk Factors for Progression of Hepatic Fibrosis

Risk Factor for Progression of Hepatic Fibrosis
Detectable HCV RNA
Hepatic fibrosis greater than stage 1*
Male sex
Obesity
Hepatic steatosis
Heavy alcohol use
Advanced age
Elevated serum alanine transaminase
Greater hepatic inflammation

*Metavir fibrosis score 1: portal fibrosis without septa formation

Table 12. Factors Predicting Response to Treatment for HCV

Major Predictors
Viral genotype other than genotype 1
Pretreatment viral load less than 600,000
Other Predictors
Female sex
Age less than 40 years
Non-Black race
Absence of bridging fibrosis or cirrhosis on liver biopsy
Body weight less than or equal to 75 kg
Absence of insulin resistance or metabolic syndrome
Elevated alanine aminotransferase (ALT) levels (3x higher than the upper limit of normal)
IL28B genotypes CC

Once the decision is made to treat patients with antiviral agents, the next step is to consider who to treat with the current standard treatment and who to treat with regimens containing sofosbuvir. The recent AASLD/IDSA guidance on simeprevir and sofosbuvir (AASLD/IDSA 2014) and other organizations (Veterans Health Administration Pharmacy Benefits 2014) *recommend against using sofosbuvir as monotherapy*.

The inclusion and exclusion criteria from published studies (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Osinusi 2013; Rodriguez-Torres 2013) may be useful in selecting patients who are more likely to have response rates closer to those reported in these studies. It is important to note that of the 10 currently published studies and the three trials added in FDA review, only two are comparative (Jacobson [NEJM] 2013a, Lawitz [NEJM]

2013). These two studies only enrolled *patients with genotype 2 and 3*. Table 13 lists the exclusion criteria from the published trials. Six of the 10 studies excluded patients with cirrhosis. The presence or absence of cirrhosis was usually based on liver biopsy within three years of trial entry, and liver biopsy is currently the standard for confirming degree of fibrosis (Bain 2004; Imbert-Bismut 2001; Parkes 2006). In the four studies including patients with cirrhosis, 15% to 35% percent of patients had cirrhosis, and none had decompensated cirrhosis (Jacobson [NEJM] 2013a; Lawitz [NEJM] 2013).

Table 13. Patient Exclusion Criteria from Published Sofosbuvir Trials

Exclusion Criteria
Age less than 18 years
HIV or HBV co-infection
Significant alcohol or drug use within the past 12 months
Excessive current alcohol use
Significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, significant renal disease (estimated glomerular filtration rate less than 60mL/min)

Treatment Summary

Although the evidence base to support use of sofosbuvir presently is poor, some clinicians, policymakers and payers may wish to develop interim treatment and coverage criteria. Potential criteria to guide the use of sofosbuvir that are consistent with current published studies are listed below with several factors to consider.

- Limit use to genotypes 2 and 3, until comparative trials available for genotype 1.
- Do not use sofosbuvir as monotherapy.
- Limit use to patients who failed or did not tolerate current standard of care regimens or in whom PEG is contraindicated.
- Confirm degree of liver fibrosis or cirrhosis prior to authorizing treatment.
- Treat only patients at greatest risk of progressing to cirrhosis (e.g., Metavir fibrosis stage greater than or equal to 2 and additional factors increasing risk of progression to cirrhosis [e.g., hepatic steatosis, men, older, elevated serum alanine transaminase, greater hepatic inflammation]).
- Consider use for patients with HIV or HBV co-infection or those post-liver transplant carefully until comparative trials are available.
- Exclude use in patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease (estimated glomerular filtration rate less than 60mL/min).

- Ensure that patients who start therapy are closely tracked to optimize full treatment and follow-up, including prevention of re-infection.

Overall Summary

Hepatitis C is estimated to affect between 1% and 2% of the US population. Although up to one-quarter of those infected can clear the virus spontaneously, in those remaining infected it can progress over the span of 10 to 30 years or more to cirrhosis, liver failure, HCC and death. The genotype HCV-1 accounts for about three-quarters of cases in the US. The current standard of care for HCV-1 involves treatment with PEG, RBV and a protease inhibitor (boceprevir and telapravir are approved for this indication in the US) and treatment of HCV-2 and HCV-3 involves use of PEG and RBV only. These interferon-based regimens have success rates of 40% to 80%, depending of the underlying characteristics of the patient being treated, including factors such as genotype, progression of liver disease, adherence to therapy, and presence of other comorbidities.

Current therapy options present substantial treatment burdens to patients ranging from side effects of drugs and complicated dosing schedules. Treatment options for HCV have been changing quickly since 2011 when protease inhibitors were first approved in the US. In December 2013, the FDA approved two new agents, sofosbuvir and simeprevir, under expedited "breakthrough" status designation which allowed the use of an intermediate trial endpoint (SVR12 instead of the previously required SVR24). There are at least two more DAAs expected to be approved in 2014 and there are other newer drugs in the development pipeline.

Although improved treatments for HCV are certainly desirable, the long course of disease progression also makes it incumbent upon policymakers and clinicians to make sure that treatments will be effective. Most currently infected patients have time available to wait for conclusive data on the effectiveness and harm profile of sofosbuvir or other new drugs before deciding on an optimal treatment regimen.

This rapid evidence review located 10 studies published in seven articles, although the majority of them were non-comparative studies and all but one was at high risk of bias. There were two comparative studies of sofosbuvir treatment for HCV-2 and HCV-3 infection, but no published comparative studies for the treatment of HCV-1. Based on the usual standards of comparative effectiveness research, currently available studies do not provide sufficient evidence for the routine use of sofosbuvir-containing regimens for the treatment of Hepatitis C infection. While initial, uncontrolled, response rates appear to be relatively high among carefully selected populations, response rates in "real world" populations are likely to be lower. Furthermore, there is evidence that relapse rates may be substantial, ranging from 5% to 28% even among patients who are fully treated with these regimens. Similarly, adverse effects have not been

studied in large numbers of patients and among those with substantial other risk factors for harms. When the first two protease inhibitors began to be used in clinical practice, the risks of adverse events approximately tripled and there could be a similar concern with these even newer drugs as they are used in widespread clinical practice.

The recently published HCV treatment guideline published by AASLD and IDSA is of poor methodologic quality and does not adhere to international or US standards for guideline development. In addition, guideline authors had substantial and multiple conflicts of interest.

Due to the lack of the usual requirement of well-designed comparative studies for approval to guide treatment and purchasing studies there is not clear evidence that this drug should be used to treat

While awaiting full disclosure of existing research and the production of more and better evidence on sofosbuvir, policymakers may decide to not allow use of or to allow very limited use of this drug. If limited use is contemplated this report details factors to consider, such as limitation to use in carefully selected HCV-2 and -3 infected individuals who are at great risk of shortly progressing to cirrhosis, and only as part of a regimen including RBV. Policymakers, clinicians and patients should remain aware of upcoming drug research and carefully examine the quality of new research as it is made available.

In addition, the evidence gaps highlighted in this review may offer an opportunity for policymakers and clinicians to advocate for improved research and to contribute to a better evidence base for decision-making. Policymakers might consider the following activities:

- Require transparency about the research. Patients, clinicians and policymakers need adequate information available in order to make good decision about the safety, effectiveness and place in treatment of sofosbuvir. True patient-centeredness requires the availability of all existing data in order for considered decisions to be made that respect patient autonomy. Public stewardship requires those same kind of data to make sure that patients are helped more than harmed and that the overall value of the treatment is worthwhile. As an example, most studies of sofosbuvir include SVR24 as a secondary outcome measure, but this information is not included in many publications. Policymakers can encourage the FDA and ask the manufacturer directly to release this data.
- Policymakers can ask the NIH to fund and the FDA to demand truly comparative studies on this and other newer drugs for Hepatitis C. Current trials do not answer the question of which therapy is best for which patient at which point in time during the disease course. Studies of these drugs should include populations that approximate the

characteristics of publically insured patients including race, stage of disease, prior treatment history, comorbid medical and behavioral health conditions.

- State policymakers may wish to cover sofosbuvir and other newer agents with the requirement of evidence development. Relatively simple data collection efforts may yield evidence more applicable to publically insured populations more rapidly than industry or federally funded research might. For example, if a state simply required submission of SVR24 as a condition of coverage, real world data on this important outcome could be obtained in less than a year.

Appendix A. Treatment Response and Relapse Rates by Genotype and Specialized Studies

Genotype	Treatment	Response	Relapse[1]	Study
Treatment Response and Relapse Rates by Genotype				
Genotype 1	SOF + PEG + RBV 12 w	SVR12: 89% (260/291)	8.6% (28/326)[2]	NEUTRINO, Lawitz 2013, (NEJM)
	Interferon-free regimens			
	SOF + RBV 12 w (tx exp)	SVR12: 10% (1/10) SVR24: 10% (1/10)	90% (9/10)	ELECTRON, Gane 2013
	SOF + RBV 12 w (tx naïve)	SVR12: 84% (21/25) SVR24: 84% (21/25)	16% (4/25)	
	SOF + RBV 24 w	SVR12: 68% (17/25) SVR24: 68% (17/25)	28% (7/25)	NIH study, Osinusi 2013
	SOF + low-dose RBV (600mg) 24 w	SVR12: 48% (12/25) SVR24: 48% (12/25)	40% (10/25)	
Genotype 2	SOF + RBV 12 w	SVR12: 95% (69/73)	5% (4/73)	FISSION, Lawitz 2013, (NEJM)
		SVR12: 82% (33/39)	18% (7/39)	FUSION, Jacobson 2013a (NEJM)
		SVR12: 93% (101/109)	5% (5/107)	POSITRON, Jacobson 2013a (NEJM)
		SVR12: 93% (68/73)	7% (5/73)	VALENCE, Mishra (FDA) 2013 ***Unpublished study***
	SOF + RBV 16 w	SVR12: 89% (31/35)	11% (4/35)	FUSION, Jacobson 2013a

Genotype	Treatment	Response	Relapse[1]	Study
				(NEJM)
Genotype 3	SOF + RBV 12 w	SVR12: 56% (102/183)	40% (72/179)	FISSION, Lawitz 2013, (NEJM)
		SVR12: 30% (19/64)	66% (42/64)	FUSION, Jacobson 2013a (NEJM)
		SVR12: 61% (60/98)	38% (37/98)	POSITRON, Jacobson 2013a (NEJM)
	SOF + RBV 16 w	SVR12: 62% (39/63))	38% (24/63)	FUSION, Jacobson 2013a (NEJM)
	SOF + RBV 24 w	SVR12: 84% (210/250)	14% (34/249)	VALENCE, Mishra (FDA) 2013 ***Unpublished study***
Genotype 4	SOF + PEG + RBV 12 w	SVR12: 96% (27/28)	*Relapse rates were not separately reported by genotype. Overall relapse rate in study 8.6% (28/326)*	NEUTRINO, Lawitz 2013, (NEJM)
Treatment Response and Relapse Rates for HCV/HIV Co-infected Patients				
Genotype 1 (tx naïve)	SOF + RBV 24 w (***interferon free regimen***)	SVR12: 76% (87/114)	22% (25/113)	PHOTON-1, Mishra (FDA) 2013 ***Unpublished study***
Genotype 2	SOF + RBV 12 w (tx naïve)	SVR12: 88% (23/26)	18% (12/67) (combines genotype 2/3)	
	SOF + RBV 24 w (tx exp)	SVR12: 93% (14/15)	7% (2/28) (combines genotype 2/3)	
Genotype 3	SOF + RBV 12 w (tx naïve)	SVR12: 67% (28/42)	18% (12/67) combines	

Genotype	Treatment	Response	Relapse[1]	Study
			genotype 2/3)	
	SOF + RBV 24 w (tx exp)	SVR12: 92% (12/13)	7% (2/28) (combines genotype 2/3)	
Treatment Response Sofosbuvir + Simeprevir Combination Study				
Genotype 1 **Cohort 1 (null response prior tx (PEG+RBV)** **Metavir score = F0-F2)**	SOF + SMV 12 w	SVR 12: 93% (13/14)	Relapse was unevenly reported in the abstracts Jacobson (2013b) reported that "3 pts in the C1/C2 12 w groups (± RBV) and 1 pt in the C1 24 w (+RBV) group" relapsed. Sulkowski (2014) reported that 3 pts in cohort 1 relapsed (tx regimen not specified) Lawitz (2014) reported that 3 pts relapsed in cohort 2 (tx regimen not specified)	COSMOS Jacobson 2013b Hepatology ***Published abstract only*** Sulkowski 2014 ***Conference presentation; excluded 5 pts included in Jacobson (2013b)***
	SOF + SMV + RBV 12 w	SVR12: 96% (26/27)		
	SOF + SMV 24 w	SVR12: 100% (14/14)		
	SOF + SMV + RBV 24 w	**SVR12: 79% (19/24)[3]**		
Genotype 1 **Cohort 2 – (null response to prior tx or tx naïve with Metavir Score F3-F4)**	SOF + SMV 12 w	SVR12: 92.9% (13/14)		Lawitz 2014 ***Conference presentation***
	SOF + SMV + RBV 12 w	SVR12: 92.9% (13/14)		
	SOF + SMV 24 w	SVR12: 92.9% (13/14)		
	SOF + SMV + RBV 24 w	SVR12: 92.9% (13/14)		

Abbreviations: Exp – experienced; NEJM – New England Journal of Medicine; NR – not reported; PEG – pegylated interferon therapy; RBV – ribavirin; unless otherwise specified, RBV refers to weight-based ribavirin, e.g. 1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg daily; SOF – sofosbuvir 400 mg daily; SMV – simeprevir 150 mg daily; SVR – sustained virologic response; tx – treatment; w – weeks

Notes

[1]Relapse is defined as a patient achieving HCV RNA < lower limit of quantitation (LLOQ) at the last measurement on treatment but subsequently having a HCV RNA ≥ LLOQ post treatment

[2]Relapse rate includes data on the 35 pts with HCV 4-6 as data was not separated out.

[3]A subsequent abstract presented at the April, 2014 European Association for the Study of the Liver (EASL) conference excluded "five patients withdrawn for non-virologic failure" and reported an SVR12 rate for this group of 90.5% (19/21) (Sulkowski 2014). No other SVR12 rates changed after excluding the patients.

Appendix B. Study Population Characteristics

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Gane, 2013 (ELECTRON)	Open label Largely a PEG regimen range study for HCV-2,3 and PEG sparing for HCV-1	25	10	18	---	42	---	---	---	---	58 (61%)	74 (78%)	---
Jacobson, 2013a (Study 1) (POSITRON)	Placebo control RCT INF tx contraindicated, unacceptable or prior discontinuation due to unacceptable AEs 12w SOF + RBV vs placebo	---	---	---	---	---	---	143	135	---	151 (54%)	254 (91%)	C: 68 (34%)
Jacobson, 2013a (Study 2) (FUSION)	Active control RCT No prior response to prior INF containing regimen Duration ranging study	---	---0	---	68	---	127	---	---	---	140 (70%)	174 (87%)	C: 44 (16%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Kowdley, 2013 (ATOMIC)	Open label RCT (Cohorts A and C) Duration ranging 12 vs 24w PEG + RBV	207	---	---	---	---	---	---	---	---	141 (68%)	[% black] 18 (9%)	F: 47 (14%)
Kowdley, 2013 (ATOMIC)	Open label NRS (Cohort B of ATOMIC with addition of NR HCV-4, 6 pts)	109	---	---	---	---	---	---	---	16	73 (58%)	[% black] 17 (14%)	See above: 23 of 47 pts with BF were in this group
Lawitz, 2013a (Lancet)	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic	121	---	---	---	---	---	---	---	---	73 (60%)	97 (80%)	F: 5 (4%)
Lawitz, 2013a (Lancet)	Additional single group study with HCV-2,3	---	---	15	---	10	---	---	---	---	16 (64%)	20 (80%)	F: 0%
Lawitz, 201b3 (Study 1) (NEJM)	Open label, single group, tx naïve, predominantly HCV-1	291	---	---	---	---	---	---	---	35	209 (64%)	257 (79%)	C: 54 (17%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
(NEUTRINO)													
Lawitz, 2013b (Study 2) (NEJM) (FISSION)	Open label non-inferiority RCT; tx naïve HCV-2, 3; 12w SOF + RBV vs PEG + RBV	3	---	137	---	359	---	---	---	---	327 (66%)	435 (88%)	100 (20%)
Osinusi, 2013 (Study 1)	Proof of concept(n=10) with HCV-1 and unfavorable tx characteristics	10	---	---	---	---	---	---	---	---	4 (40%)	1 (10%)	F: [Knodell HAI fibrosis score 3 to 4] 1 (10%)
Osinusi, 2013 (Study 2)	Open label RCT with HCV-1 and unfavorable tx characteristics	50	---	---	---	---	---	---	---	---	33 (66%)	7 (14%)	F: [Knodell HAI fibrosis score 3 to 4] 13 (26%)
Rodriguez-Torres, 2013	Blinded RCT; tx naïve with HCV-1; dose ranging	63	---	---	---	---	---	---	---	---	43 (68%)	57 (90%)	F: 4 (6 %)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Unpublished Trial Included in FDA Review													
FDA (Mishra 2013) VALENCE	Open label trial; tx naïve with HCV 2 or 3 SOF + RBV for 12 w (HCV-2) SOF + RBV for 24 w (HCV 3)	---	---	91	---	317	---	---	---	---	250 (60%)	393 (94%)	C: 88 (21%)
TOTALS (from above trials)	n/a	879	16	261	68	728	127	143	135	51	n/a	n/a	n/a
Unpublished Trial Included in FDA Review on HCV and HIV Coinfected Patients													
FDA (Mishra 2013) PHOTON-1	Open label dose ranging study in patients **with HIV-1 diagnosis** Total n = Tx naïve HCV 2-3: SOF + RBV 12 w	114	---	26	24	42	17	---	---	---	185 (83%)	153 (69%)	C: 22 (10%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
	Tx experienced HCV 2-3 or HCV 1 SOF + RBV 24 w												

Abbreviations: AEs – adverse events; HAI – histology activity index; HCV – hepatitis C virus; INT – interferon; n/a – not applicable; NR – not reported; NRS – not reported study; PEG – pegylated interferon therapy; RBV – ribavirin; unless otherwise specified, RBV refers to weight-based ribavirin, e.g. 1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg daily; RCT – randomized controlled trial; SOF – sofosbuvir 400 mg daily; tx – treatment; w – weeks

Appendix C. Evidence Tables

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Gane, 2013	Open label Largely a PEG regimen range study for HCV-2, 3 and PEG sparing for HCV-1 N=95 *Group 1* n=10 *Group 2* n=9 *Group 3* n=10 *Group 4* n=11 *Group 5* n=10 *Group 6*	Inclusion • Age ≥ 19 • HCV RNA > 50,000 IU/mL • For groups 1 to 6, HCV-2 or 3 and tx naïve • For group 7, HCV-1, prior tx failure • For group 8, HCV-1, tx naïve Exclusion • Cirrhosis • HIV or HBV positive	*Group 1; Group 2; Group 3; Group 4; Group 5; Group 6; Group 7; Group 8* Male n (%) 8 (80) 5 (56) 5 (50) 9 (82) 4 (40) 5 (50) 7 (70) 15 (60) Race n (%) *White* 7 (70) 4 (44) 8 (80) 9 (82) 4 (40) 5 (50) 9 (90) 20 (80)	Intervention 8 arm trial, all pts rec'd SOF in different regimen Groups 1 to 6, all HCV-2 or 3 and tx naïve *Group 1* SOF 400 mg/d + weight based RBV/d for 12w *Group 2* SOF 400 mg/d + RBV for 12w + PEG 180µg/w for 4w *Group 3* SOF 400 mg/d + RBV for 12w + PEG 180µg/w	Outcomes • SVR 24 • Adverse events Findings **SVR 24** n (%, 95%CI) *Group 1* 10 (100, 69 to 100) *Group 2* 9 (100, 66 to 100) *Group 3* 10 (100, 69 to 100) *Group 4* 11 (100, 72 to 100) *Group 5* 6 (60, 26 to 88) *Group 6* 9 (90, 66 to 100)	Gilead sponsored, analyzed data and prepared final version of report Not a controlled trial as all pts rec'd SOF. 4 groups (2 HCV-2/3 and 2 HCV-1) did not also get PEG Small sample size, not designed to statistically test outcomes Race is reported only as percentage

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	n=10 *Group 7* n=10 *Group 8* n=25		<u>Age</u> <u>mean (range)</u> 47 (36 to 53) 48 (29 to 66) 49 (30 to 62) 46 (37 to 57) 43 (22 to 58) 39 (19 to 54) 48 (30 to 58) 49 (22 to 69) <u>BMI</u> <u>mean (range)</u> 28 (24 to 36) 26 (21 to 32) 25 (18 to 33) 24 (21 to 28) 26 (18 to 39) 25 (21 to 35) 28 (20 to 36) 26 (19 to 38) <u>HCV RNA log_{10}IU/mL</u> <u>mean (range)</u> 6.7 (5.7 to 7.1) 6.6 (5.6 to 7.4)	for 8w *Group 4* SOF 400 mg/d + RBV for 12w + PEG 180µg/w for 12w *Group 5* SOF 400 mg/d for 12w *Group 6* SOF 400 mg/d + RBV + PEG for 8w *Group 7* HCV-1 with prior tx failure SOF 400 mg/d + RBV for 12w *Group 8* HCV-1 tx naïve SOF 400 mg/d + RBV for 12w	*Group 7* 1 (10, 0 to 45) *Group 8* 21 (84, 64 to 96) **Adverse events** n (%) *Grade 3 anemia* 17 (17.9%) *Grade 3 or 4 lymphopenia* 4 (4.2%) *Grade 3 or 4 neutropenia* 12 (12.6%) *Grade 3 leukopenia* 5 (5.3%) Authors state reduced hemoglobin levels more common in pts receiving PEG than those w/o,	white with no further details

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6.5 (5.5 to 7.2) 6.5 (5.2 to 7.3) 5.9 (4.6 to 7.4) 6.0 (4.3 to 7.3) 7.0 (5.6 to 7.5) 6.2 (4.4 to 7.2) <u>HCV-2 (Groups 1 to 6) n (%)</u> 4 (40) 3 (33) 4 (40) 4 (36) 3 (30) 0 <u>HCV-3 (Groups 1 to 6) n (%)</u> 6 (60) 6 (67) 6 (60) 7 (64) 7 (70) 10 (100)	<u>Follow-up</u> 24w post tx	but no statistical analysis	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			HCV-1a (Groups 7 to 8) n (%) 9 (90) 22 (88) HCV-1b (Groups 7 to 8) n (%) 1 (10) 3 (12) IL28B genotype n (%) *CC* 5 (50) 4 (44) 4 (40) 4 (36) 2 (20) 3 (30) 2 (20) 11 (44) *CT* 4 (40) 4 (44) 4 (40) 5 (45) 6 (60)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (60) 5 (50) 12 (18) *TT* 1 (10) 1 (11) 2 (20) 2 (18) 2 (20) 1 (10) 3 (30) 2 (8) <u>Loss to follow-up</u> 1 pt, group 6			
Jacobson , 2013a (study 1) POSITRON study	Placebo control RCT Interferon tx contraindicated, unacceptable or prior discontinuation due to unacceptable	<u>Inclusion</u> • Age ≥ 18 • HCV-2 or 3 • HCV RNA ≥ 104 IU/mL • BMI ≥ 18 kg/m2 • Discontinuation of previous interferon tx due to AE OR ineligible for interferon tx OR declined interferon tx • Up to 20% with	*Placebo; Intervention* <u>Age</u> <u>mean (range)</u> 52 (28 to 67) 52 (21 to 75) <u>BMI</u> <u>mean (range)</u> 28 (20 to 43) 28 (18 to 53)	<u>Intervention</u> SOF 400 mg/d and RBV 1000 to 12000 mg/d for 12w <u>Comparator</u> Placebo <u>Follow-up</u> 24w post tx	<u>Outcomes</u> • SVR 4 post tx • SVR 12 post tx • Relapse • Adverse events <u>Findings</u> n (%) **SVR 4 post tx** *Intervention* 172/207 (83%), 204 returned for	Gilead sponsored, analyzed data and prepared final version of report 63 sites in US, Canada, Australia, New

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	AEs N=278 *Intervention* n=207 *Comparator* n=71	compensated cirrhosis • ECG w/o abnormalities • AAT ≤ 10 x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for men and ≥ 11 g/dL for women • Albumin ≥ 3 g/dL • Direct bilirubin ≤ 1.5 x ULN • HbA1c ≤ 10% • Creatine clearance ≥ 60mL/min • INR ≤ 1.5 x ULN • No investigational drug w/i 30d • Contraception <u>Exclusion</u> • Prior exposure to a direct-acting anti-viral targeting HCV NS5B polymerase • Pregnant/nursing/pregnant partner • Other clinically significant chronic liver disease • HIV or HBV positive	<u>Male n (%)</u> 34 (48%) 117 (57%) <u>Race n (%)</u> *White* 66 (93%) 188 (91%) *Black* 4 (6%) 9 (4%) *Hispanic* 11 (15%) 19 (9%) <u>HCV-2 n (%)</u> 34 (48%) 109 (53%) <u>HCV-3 n (%)</u> 37 (52%); 98 (47%) <u>IL28B genotype n (%)</u> *CC* 29 (41%)	6 pts (2.9%) did not complete tx, 2 pts lost to follow-up	visit *Placebo* 0/71 (0%), 71 returned for visit **SVR 12 post tx** n (%, 95% CI) *Intervention* 161/207 (78, 72 to 83) (only 171/207 pts returned for 12w post follow-up) **Factors significantly associated with SVR 12** *Sex (female vs male)* OR 2.668 (95% CI, 1.198 to 5.940) p=0.0163	Zealand Only reports SVR 12 Note that at the end of tx, all pts in intervention group showed HCV RNA < 25 IU/mL but by week 12 after tx had dropped to 78%. 22% had relapsed. What would happen by week 24?

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Contraindications to RBV therapy • Chronic use of immunosuppressive agents • Significant drug or alcohol abuse w/i 12m • Excessive alcohol consumption • Hx of malignancy, clinically significant hemoglobinopathy, solid organ transplantation, clinical hepatic decompensation, primary gastrointestinal disorder, significant pulmonary or cardiac disease or porphyria, or other serious clinical condition • Hx of difficulty with blood collection or venous access • Donation or loss of > 400mL of blood w/i 2m	97 (47%) *CT* 36 (51%) 84 (41%) *TT* 6 (8%) 26 (13%) Cirrhosis n (%) 13 (18%) 31 (15%) Baseline ALT > 1.5 x ULN 42 (59%) 117 (57%) INF tx classification *Unacceptable AE* 8 (11%) 17 (8%) *Contraindicated* 33 (46%) 88 (43%)		*HCV-2 vs HCV-3* OR 8.659 (95% CI, 3.616 to 20.732) p<0.0001 *Duration of prior HCV tx (>12w vs no tx)* OR 0.131 (95% CI 0.038 to 0.452) p<0.0013 **Relapse** 42 pts relapsed after stopping tx (42/207 = 20.3%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Pts decision 30 (42%) 102 (49%) <u>Response to previous tx</u> *No response* 2 (3%) 2 (1%) *Relapse* 4 (6%) 11 (5%)			
Jacobson , 2013a (Study 2) FUSION study	Active control RCT No prior response to prior INF containing regimen N=201 *Group 1* n=103	<u>Inclusion</u> • Age ≥ 18 • HCV-2 or 3 • Prior tx failure with INF for ≥ 12w (non-response or relapse/breakthrough) • Up to 30% with compensated cirrhosis • HCV RNA ≥ 104 IU/mL • BMI ≥ 18 kg/m2 • ECG w/o abnormalities • Discontinuation of previous INF tx due to AE *or* ineligible	*Group 1, Group 2* <u>Age</u> <u>mean (range)</u> 54 (30 to 69) 54 (24 to 70) <u>BMI</u> <u>mean (range)</u> 28 (19 to 43) 29 (20 to 44) <u>Male n (%)</u> 73 (71%)	<u>Group 1</u> SOF 400 mg/d and RBV 1000 to 1200 mg/d for 12w then 4w of placebo <u>Group 2</u> SOF 400 mg/d and RBV 1000 to 1200 mg/d for 16w 1 pt in group 1	<u>Outcomes</u> • SVR 4w post tx • SVR 12w post tx • Relapse • Adverse events <u>Findings</u> n (%) **SVR 4 post tx** *Group 1* 56/100 (56%), 99 returned for visit	Gilead sponsored, analyzed data and prepared final version of report

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	Group 2 n=98	for interferon tx OR declined interferon tx • Up to 20% with compensated cirrhosis • AAT ≤ 10 x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for men and ≥ 11 g/dL for women • Albumin ≥ 3 g/dL • Direct bilirubin ≤1.5 x ULN • HbA1c ≤ 10% • Creatine clearance ≥ 60mL/min • INR ≤ 1.5 x ULN • Platelets ≥ 50,000 µL • No investigational drug w/i 30 days • Contraception <u>Exclusion</u> • Prior exposure to direct-acting anti-viral targeting HCV NS5B polymerase • Pregnant/nursing/pregnant partner	67 (68%) <u>Race n (%)</u> *White* 88 (85%) 86 (88%) *Black* 5 (5%) 1 (1%) *Hispanic* 10 (10%) 8 (8%) <u>HCV-1 n (%)</u> 3 (3%) 3 (3%) <u>HCV- 2 n (%)</u> 36 (35%) 32 (33%) <u>HCV-3 n (%)</u> 64 (62%) 63 (64%)	discontinued tx due to AE, 2 pts in group 1 lost to follow-up	*Group 2* 73/95 (77%), 95 returned for visit **SVR 12 post tx** *Group 1* 50/100 (50%), 54 returned for visit *Group 2* 69/95 (73%), 73 returned for visit **Factors associated with SVR 12 for Group 1** *HCV- 2 vs HCV- 3* OR 21.486 (95% CI, 6.144 to 75.142) p<0.0001 *Baseline weight-based RBV dose* OR 1.469 (95% CI, 1.089 to 1.983) p=0.0119	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Other clinically significant chronic liver disease • HIV or HBV positive • Contraindication to RBV tx • Chronic use of immunosuppressive agents • Significant drug or alcohol abuse w/i 12m • Hx of malignancy, clinically significant hemoglobinopathy, solid organ transplantation, clinical hepatic decompensation, primary gastrointestinal disorder, significant pulmonary or cardiac disease or porphyria, or other serious clinical condition • Excessive alcohol consumption • Hx of difficulty with blood collection or venous access • Donation or loss of > 400mL of blood w/i 2m	<u>IL28B genotype n (%)</u> *CC* 31 (30%) 30 (31%) *CT* 53 (51%) 56 (57%) *TT* 19 (18%) 12 (12%) <u>Cirrhosis n (%)</u> 36 (35%) 32 (33%) <u>Response to previous tx</u> <u>n (%)</u> *No response* 25 (24%) 25 (26%) *Relapse* 78 (76%) 73 (74%)		*Cirrhosis (no vs yes)* OR 3.117 (95% CI 1.019 to 9.537) p=0.0463 **Factors associated with SVR 12 for Group 2** *HCV- 2 vs HCV-3* OR 10.522 (95% CI 2.251 vs. 49.174) p=0.0028 *Female vs male* OR 3.978 (95% CI, 1.169 to 13.539) p=0.0271 **Relapse** 73 pts relapsed after stopping tx (73/201, 36.3%), *no details provided*	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Kowdley, 2013	Open label Duration ranging 12w vs 24w PEG + RBV N=332 *Cohort A* n=52 (HCV-1) *Cohort B* n=125 (HCV-1 = 109; HCV-4 = 11; HCV-6 = 5) *Cohort C* n=155 (HCV-1)	<u>Inclusion</u> • Age ≥ 18 • HCV-1, 4, 5 or 6 • Tx naïve • HCV RNA ≥ 50,000 IU/mL <u>Exclusion</u> • Cirrhosis or other chronic liver disease • BMI ≤ 18 kg/m2 • HIV or HBV positive	*Cohort A; Cohort B; Cohort C except where noted* <u>Age</u> <u>(mean ± sd)</u> 51 ± 9.8 50 ± 11 50 ± 10.8 <u>Male n (%)</u> 35 (67%) 73 (58%) 106 (68%) <u>Race n (%)</u> *Black* 2 (4%) 17 (14%) 16 (10%) *Non-black* 50 (96%) 108 (86%) 139 (10%)	<u>Intervention</u> *Cohort A* SOF 400 mg/d + weight based RBV/d + PEG 180µg/w for 12w *Cohort B* SOF 400 mg/d + RBV/d + PEG/w for 24w *Cohort C* SOF 400 mg/d + RBV/d + PEG for 12w then 50% rec'd SOF mono tx for 12w; 50% rec'd SOF + RBV for 12w <u>Follow-up</u> 24w	<u>Outcome</u> • SVR 24 • Adverse events <u>Findings</u> **SVR 24 for HCV-1** n (%, 95% CI) *Cohort A* 46/52 (89, 77 to 96) *Cohort B* 97/109 (89, 82 to 94) *Cohort C* 135/155 (87, 81 to 92) **SVR 24 for HCV-4** n (%, 95% CI) *Cohort B* 9/11 (82, 48 to 98) **SVR 24 for HCV-6** n (%, 95% CI) *Cohort B*	Gilead sponsored, analyzed data and prepared final version of report Pooled efficacy data for Cohort C's 2 extended tx arms Per-protocol analysis also included in article

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Hispanic 10 (19%) 26 (21%) 31 (20%) <u>BMI</u> <u>(mean ± sd)</u> 27.2 ± 4.6 27.6 ± 5.0 28.4 ± 4.6 <u>HCV RNA log_{10} IU/mL</u> <u>(mean ± sd)</u> 6.5 ± 0.7 6.3 ± 0.7 6.4 ± 0.8 <u>HCV-1a, 1b, 4, 6</u> <u>n (%)</u> *Cohort A* 40 (77%) 12 (23%) 0 0 *Cohort B* 85 (68%)		5/5 (100, 48 to 100) **Difference in SVR 24 for HCV-1 by regime** A to B: p=0.94 A to C: p=0.78 **Relapse** *Cohort A* 2 (4%) *Cohort B* 1 (1%) *Cohort C* 4 (3%) **Adverse events** 13 serious AEs in 12 pts *9 adverse events reported t as "non-tx related"* arrythemia, ischaemic colitis,	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			24 (19%) 11 (19%) 5 (4%) *Cohort C* 116 (75%) 39 (25%) 0 0 <u>IL28B genotype n (%)</u> *CC* 13 (25%) 36 (29%) 39 (25%) *CT* 33 (64%) 63 (50%) 88 (57%) *TT* 6 (12%) 26 (21%) 28 (18%)		chest pain, acute cholecystitis, cholelithiasis, alcohol poisoning, road traffic accident, costochondritis, hip arthroplasty *4 adverse events reported as related to PEG and RBV but not SOF* anemia, auto-immune hepatitis, pyelonephritis, pancytopenia	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			No/minimal fibrosis n (%) 9 (17%) 14 (11%) 20 (13%) Portal fibrosis n (%) 36 (69%) 93 (74%) 99 (64%) Bridging fibrosis n (%) 7 (14%) 17 (14%) 23 (15%) Loss to f/u n (%) 26 (7.8%) *Cohort A* 4 (7.7%) *Cohort B* 13 (10.4%) *Cohort C* 9 (5.8%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Lawitz , 2013a (Lancet)	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic N=147 *Cohort A* n=122 Group 1 n=48 Group n=48 Group 3 n=26 *Cohort B* n=25	Inclusion • Age ≥ 18 • HCV-1, 2 or 3 • Tx naïve • HCV RNA ≥ 50,000 IU/mL • Neutrophil count 1-5 x 109/L or ≥ 1-25 x 109/L for black patients • Hb ≥ 11 g/dL for women or ≥ 12 g/dL for men • Platelets ≥ 90x109/L • Total bilirubin ≤ 2xULN • Albumin ≤ 30 g/L Exclusion • Cirrhosis • HIV or HBV positive • Hx of psychiatric illness, pulmonary or cardiac disease, seizure disorder or other serious comorbid condition	*Cohort A (Group 1, Group 2, Group 3)* Age (mean ± sd) 48.4 ± 11.5 51.4 ± 9.4 48.6 ± 9.4 Male n (%) 33 (69%) 21 (45%) 19 (73%) Race n (%) *White* 39 (81%) 37 (78%) 21 (80%) *Black* 6 (13%) 7 (15%) 5 (19%) *Hispanic* 5 (10%)	Intervention *Cohort A* HCV-1 randomized 2:2:1 to 3 protocols in 2 steps. 1st step for 12w *Group 1* SOF 200 mg/d + weight based RBV/d + 180µg PEG weekly *Group 2* SOF 400 mg/d + RBV/d + PEG weekly *Group 3* Placebo + RBV + PEG If pts achieved eRVR (HCV RNA ≤ 15 IU/mL) in	Outcomes • Primary outcome – safety and tolerability • "study was not designed to statistically test efficacy" (p.403) • Secondary outcomes o RVR 4 o SVR 12 o SVR 24 Findings **Adverse Events** (Cohorts A & B) *Common side effects* Fatigue, headache, nausea, chills, pain, insomnia Fatigue, rash,	Gilead sponsored, analyzed data and prepared final version of report Placebo group (Cohort A, PEG-INF + RBV + placebo) very small (n=26)

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (13%) 1 (4%) <u>BMI</u> <u>(mean ± sd)</u> 26.6 ± 3.4 26.8 ± 4.5 28.6 ± 4.1 <u>HCV RNA IU/mL</u> <u>(mean ± sd)</u> 6.5 ± 0.6 6.4 ± 0.8 6.5 ± 0.8 <u>HCV-1a n (%)</u> 37 (77%) 35 (74%) 20 (77%) <u>HCV-1b n (%)</u> 11 (23%) 12 (26%) 6 (23%) <u>IL28B genotype n (%)</u> *CC*	weeks 4 to 12, pts rec'd 12w of PEG + RBV If placebo or failure to achieve eRVR, pts rec'd 36w PEG + RBV *Cohort B* HCV-2 or -3 SOF 400 mg + RBV + PEG for 12w	fever, diarrhea "more common" in SOF groups than placebo (no p value) Headache more common in placebo group (no p-value) 3 pts in SOF regimens developed level 3 increase in AST levels 8 pts in Cohort A discontinued tx due to AE *Group 1* 2 pts – neutropenia, folliculitis *Group 2* 3 pts – aphthous	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			21 (44%) 18 (38%) 11 (42%) *CT* 24 (50%) 19 (40%) 11 (42%) *TT* 3 (6%) 10 (21%) 4 (15%) <u>No/minimal fibrosis n (%)</u> 12 (25%) 7 (15%) 3 (12%) <u>Portal fibrosis n (%)</u> 35 (73%) 38 (81%) 21 (81%)		ulcer; MI; depression & suicidal ideation Post SOF, 3 pts with severe AE: retinal vein occlusion; lynphangitis; chest pain & ECG ST segment elevation **RVR 4** n (%, 95% CI) *Cohort A* Group 1 47 (98, 89 to 100) Group 2 46 (98, 89 to 100) Group 3 5 (19, 7 to 39) *Cohort B* 24 (96, 80 to 100)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Bridging fibrosis n (%) 1 (2%) 2 (4%) 2 (8%) Loss to follow-up 2 *Cohort B* Age (mean ± sd) 47.2 ± 11.1 Male n (%) 16 (64%) Race n (%) *White* 20 (80%) *Black* 4 (16%) *Hispanic* 1 (4%) BMI (mean ± sd)		**SVR 12** n(%, 95% CI) *Cohort A* Group 1 43 (90, 77 to 97) Group 2 43 (91, 80 to 98) Group 3 15 (58, 40 to 77) *Cohort B* 23 (92, 74 to 99) **SVR 24** n (%, 95% CI) *Cohort A* Group 1 41 (85, 72 to 94) Group 2 42 (89, 77 to 96) Group 3 15 (58, 40 to 77)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			28.6 ± 4.8 <u>HCV RNA IU/mL (mean ± sd)</u> 6.1 ± 0.8 <u>HCV-2 n (%)</u> 15 (60%) <u>HCV-3 n (%)</u> 10 (40%) <u>IL28B genotype n (%)</u> *CC* 7 (28%) *CT* 17 (68%) *TT* 1 (4%) <u>No/minimal fibrosis n (%)</u> 7 (28%) <u>Portal fibrosis n (%)</u> 18 (72%)		*Cohort B* 23 (92, 74 to 99)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Loss to follow-up 1			
Lawitz, 2013b (NEJM) (Study 1) NEUTRINO study	Open label; single group; tx naïve; 89% HCV-1 (11% HCV-4, 5, 6); 17% cirrhotic N=327	Inclusion • Age ≥ 18 • HCV-1,4,5, or 6 • HCV RNA ≥ 10,000 IU/mL • HCV tx naïve • Up to 20% of pts could have evidence of cirrhosis • BMI ≥ 18 kgm2 • ALT ≤ 10x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for males, ≥ 11 g/dL for females • White blood cell count ≥2500/µL • Absolute neutrophil count ≥1500/µL (or≥ 1000/µL if considered a physiologic variant in a subject of African descent) • Platelets ≥ 90,000/µL • INR ≤ 1.5 x ULN unless subject has known hemophilia or is stable on an	Age mean (range) 52 (19 to 70) Male n (%) 209 (64%) Race n (%) *White* 257 (79%) *Black* 54 (17%) *Hispanic* 46 (14%) HCV-1a n (%) 225 (69%) HCV-1b n (%) 66 (20%) HCV-4 n (%) 28 (9%)	Intervention SOF 400 mg/d, weight based RBV daily (1000mg < 75kg or 1200mg ≥ 75kg), and PEG alfa 2a 180 µg weekly for 12w Comparator *None* Follow up 12w post tx	Outcomes • SVR 12 post tx Findings n (%, 95% CI) **SVR 12** *Overall* 295/327 (90.2, 87 to 93) No significant difference in SVR by genotype or race *Cirrhosis* 43/54 (79.6, 67 to 89) *No cirrhosis* 252/273 (92.3, 88.5 to 5.2) (no p value)	Gilead sponsored, analyzed data and prepared final version of report

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		anticoagulant regimen affecting INR • Albumin ≥ 3 g/dL • Direct bilirubin ≤ 1.5 x ULN • Thyroid-stimulating hormone (TSH) ≤ ULN • HgbA1c ≤ 10% • Creatinine clearance ≥ 60 mL/min, as calculated by the Cockcroft-Gault equation • No investigational study participation w/i 30 days • Contraception <u>Exclusion</u> • Prior tx for HCV with an INF or RBV • Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase • Pregnant/nursing/pregnant partner • Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, α1 antitrypsin	<u>HCV-5 n (%)</u> 1 (<1%) <u>HCV-6 n (%)</u> 6 (2%) <u>BMI</u> <u>Mean (range)</u> 29 (18 to 56) <u>Mean HCV RNA log_{10} UL/mL</u> <u>(mean ± sd)</u> 6.4 ± 0.7 <u>HCV RNA ≥ 800,000 IU/mL</u> <u>n (%)</u> 267 (82% <u>IL28B genotype</u> <u>n (%)</u> *CC* 95 (29%) *CT* 181 (55%)		*IL28B GT CC* 93/95 (97.9, 92.6 to 99.7) *IL28B GT non-CC* 202/232 (87.%,82.1 to 91.1) (no p value) **Adverse events** *Any AE* 310/327 (95%) 5 pts (2%) discontinued due to AE 4 pts (1%) serious AE (not specified)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		deficiency, cholangitis) • HIV or HBV positive • Contraindications for PEG or RBV therapy • Pre-existing significant psychiatric conditions including severe depression, severe bipolar disorder, and schizophrenia. Other psychiatric disorders are permitted if the condition is well controlled with a stable tx regimen for ≥ 1 yr from screening • Hx of autoimmune disorders, severe chronic obstructive pulmonary disease, significant cardiac disease, clinically significant retinal disease, clinically significant malignancy diagnosed or treated w/i 5 yrs, solid organ transplantation, hepatic decompensation, gastrointestinal disorder,	*TT* 51 (16%) Cirrhosis n (%) 54 (17%) AAT ≥ 1.5xUL n (%) 166 (51%) Loss to follow-up n (%) 2 (0.6%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		porphyria, or other major illness. • Chronic use of systemically administered immunosuppressive agents • Clinically relevant drug or alcohol abuse w/i 12m of screening • Excessive alcohol ingestion • Hx of difficulty with blood collection and/or poor venous access for the purposes of phlebotomy • Donation or loss of >400 mL of blood w/i 2m prior to baseline/day 1 • Use of any prohibited concomitant medications w/i 28d of the baseline/day 1 visit • Known hypersensitivity to PEG, RBV, the study investigational medicinal product, the metabolites, or formulation excipients				

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Lawitz , 2013b (NEJM) (Study 2) FISSION study	Open label RCT tx naïve; HCV-2, 3; 20% cirrhotic N=499 *Intervention* n=256 *Comparator* n=243	Inclusion • Age ≥ 18 • HCV-2 or 3 • HCV RNA ≥ 10,000 IU/mL • HCV tx naïve • Up to 20% of pts can have evidence of cirrhosis • BMI ≥ 18 kg m2 • Contraception Exclusion • HIV or HBV positive • Hx of clinically significant chronic liver disease, consistent decompensated liver disease, psychiatric illness, immunologic disorder, hemoglobinopathy, pulmonary disease (including pneumonia or pneumonitis), cardiac disease, seizure disorder or anticonvulsant use, poorly controlled diabetes, or cancer, malignancy, acute	*Intervention; comparator* Age mean (range) 48 (20 to 72) 48 (19 to 77) Male n (%) 171 (67%) 156 (64%) Race n (%) *White* 223 (87%) 212 (87%) *Black* 12 (5%) 5 (2%) *Hispanic* 41 (16%) 31 (13%) Genotype n (%) *HCV-2* 70 (27%)	Intervention SOF 400mg/d and weight based RBV for 12w Comparator PEG alfa2a 180 µg weekly and 800 mg/d RBV for 24w Follow-up 12w post tx	Outcomes • SVR 12 post tx Findings **SVR 12 post tx** 67% (170/253) vs 67% (162/243) **Relapse pts who completed tx** 29% (71/242) vs 20% (37/188) **Relapse pts who did not complete tx** 43% (3/7) vs 31% (9/29) **Total relapse** 74/249 (29.7%) vs 46/217 (21.2%) **SVR 12 by genotype** *Intervention* 97% of pts with	Gilead sponsored, analyzed data and prepared final version of report Comparator group rec'd a lower dose of RBV than SOC (800mg vs weight-based dose)

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		pancreatitis with elevated lipase, uncontrolled thyroid disease or abnormal TSH levels or solid organ transplantation • Clinically significant ECG • Active substance abuse, • Abnormal hematologic and biochemical parameters, including: a) neutrophil count < 1500 cells/mm3 (or < 1250 cells/mm^3 for African-American/black subjects or cirrhotic patients); b) Hb < 11 g/dL in females or <12 g/dL in males; c) Platelet count ≤ 90,000 cells/mm^3 (noncirrhotic) or ≤ 75,000 cells/mm^3 (cirrhotic); d) creatinine ≥ 1.5 x ULN; e) estimated glomerular filtration rate, calculated by the Chronic Kidney Disease-Epidemiology Collaboration equation, < 60 mL/min/1.73	67 (28%) *HCV-3* 183 (71%) 176 (72%) BMI mean (range) 28 (17 to 51) 28 (19 to 52) HCV RNA log_{10} UL/mL (mean ± sd) 6.0 ± 0.8 6.0 ± 0.8 HCV RNA ≥ 800,000 IU/mL n (%) 145 (57%) 157 (65%) IL28B genotype n (%) *CC* 108 (42%) 106 (44%)		HCV-2, 56% of pts with HCV-3 *Comparator* 78% of HCV-2, 63% of HCV-3 (*no p-values or CIs reported*) **SVR 12 by pts with cirrhosis at baseline n=50 both groups:** 47% vs 38% (*no p-values or CIs reported*) **Adverse Events** *Any AE* 220/256 (86%) vs 233/243 (96%) *Discontinuation due to AE* 3 (1%) vs 26 (11%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		m^2;f) ALT or AST ≥ 10 x ULN; g) total bilirubin ≥ 1.5 x ULN (except patients with Gilbert's syndrome); h) albumin ≤ 3.2 g/dL 11 • Donation or loss of >400 mL of blood w/i 2m prior to first dose administration • Hx of clinically significant drug allergy to nucleoside/nucleotide analogs • Systemic antineoplastic or radiation therapy w/i 6m prior to the first dose of study drug or the expectation that such tx will be needed at any time during the study • Subjects receiving oral or intravenous strong p-glycoprotein inhibitors (including cyclosporine, quinidine, dronedarone, itraconazole, verapamil, or ritonavir) w/i 28d of dosing	*CT* 121 (47%) 98 (40%) *TT* 25 (10%) 38 (16%) <u>Cirrhosis n (%)</u> 50 (20%) 50 (21%) <u>AAT ≥ 1.5xULN n (%)</u> 138 (54%) 146 (60%) <u>Loss to follow-up n (%)</u> 1 (0.3%) 1 (0.03%)		*Serious AEs (not specified)* 7 (3%) vs 3 (1%) *Specific AEs* Influenza/fever 3 % vs 16 to 18%% Depression 5% vs 14% Hemoglobin < 10g/dcl 9% vs 14% Neutrophil count 500 to 700 mm^3 0% vs 12% Neutrophil count < 500 0% vs 2% Decreased lymphocyte, platelet, white cell counts 0% vs 1 to 7%	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Participation in a clinical study with an investigational drug, biologic, or device w/i 3m prior to first dose administration • Pregnant/nursing/pregnant partner • Poor venous access making the pt unable to complete the required laboratory testing schedule				
Osinusi, 2013 (Study 1)	Proof of concept with HCV-1 and unfavorable tx characteristics N=10	<u>Inclusion</u> "pts with unfavorable tx characteristics" • HCV-1 • Tx naïve • Neutrophil count ≥ 750 cells µL • Platelet count ≥ 50,000 cells/µL • Hb ≥ 11 g/dL (women) or ≥ 12 g/dL (men) • HIV negative • HBV negative	<u>Age</u> <u>median (range)</u> 54 (50 to 57) <u>Men n (%)</u> 4 (40%) <u>BMI</u> <u>median (range)</u> 26 (26 to 34) <u>Race n (%)</u> *Black* 9 (90%)	<u>Intervention</u> SOF 400 mg/d and weight based RBV daily (<75 kg= 400 mg RBV am and 600 mg pm; >75 kg = 600 mg RBV both am and p.m.) for 24w <u>Follow-up</u> 24w post tx	<u>Findings</u> **SVR 24** 9/10 (90%)	None

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			White 1 (10%) *Hispanic* 0 <u>IL28B genotype</u> <u>n (%)</u> *CC* 3(33%) *CT/TT* 6(67%) <u>Knodell HAI fibrosis</u> <u>score n (%)</u> *0 to 1* 9 (90%) *3 to 4* 1 (10%) <u>HCV-1a n (%)</u> 6/10 (60%) <u>HCV-1b n (%)</u> 4/10 (40%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Osinusi, 2013 (Study 2)	Open label RCT with HCV-1 and unfavorable tx characteristics N=50 *Group 1* n=25 *Group 2* n=25	Inclusion "pts with unfavorable tx characteristics" • HCV-1 • Tx naïve • Neutrophil count ≥ 750 cells µL • Platelet count ≥ 50,000 cells/µL • Hemoglobin ≥ 11 g/dL (women) or ≥ 12 g/dL (men) • HIV negative • HBV negative	*Group1, Group2* Age median (range) 54 (51 to 56) 55 (48 to 59) Men n (%) 19 (76%) 14 (56%) BMI median (range) 28 (25 to 31) 30 (27 to 37) Race n (%) *Black* 18 (72%) 23 (92%) *White* 5 (20%) 2(8%) *Hispanic* 2(8%)	Intervention *Group 1* SOF 400mg/d and weight based RBV for 24w *Group 2* SOF 400 mg/d and RBV 600 mg/d for 24w Follow-up 24w post tx	Outcomes • SVR 24 post tx • HCV RNA < level of quantification • Safety and tolerability Findings n (%, 95% CI) **SVR 24 post tx** *Group 1* NR (68, 46 to 85) *Group 2* NR (48, 28 to 69) **HCV RNA level < level of quantification** *Group 1* Week 24 24 (96, 80 to 100) 24w post tx 17 (68, 46 to 85)	5/33 authors report relationship to Gilead, including three Gilead employees

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			0 <u>IL28B genotype</u> <u>n (%)</u> *CC* 4(16%) 4(16%) *CT/TT* 21(84%) 21(84%) <u>Knodell HAI fibrosis score</u> <u>n (%)</u> *0 to 1* 19 (76%) 18 (72%) *3 to 4* 6 (24%) 7 (28%) <u>HCV-1a n (%)</u> 20 (80%) 16 (64%)		*Group 2* Week 24 22 (88, 69 to 97) 24w post tx 12 (48, 28 to 69) **Characteristics associated with relapse** *Male* OR 6.09, 95% CI 1.17 to 31.6, p=0.03 *Advanced fibrosis* OR 4.27, 95% CI 1.10 to 16.54, p=0.04 *Baseline HCV RNA ≥ 800,000 IU/mL* OR 5.74, 95% CI 1.35 to 24.38, p=0.02	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			HCV-1b n (%) 5 (20%) 9 (36%)		**Adverse Events** *Common* Headache, anemia, fatigue, nausea *Grade 3 events* 6 total Group 1 Hyperbilirubinemia 1 (4%) Group 2 Anemia 1 (4%) Hypophosphatemia 2 (8%) Neutropenia 1 (4%) Nausea 1 (4%)	
Rodriguez, 2013	Randomized, placebo controlled, double-blind	Inclusion • Age 18 to 65 • HCV-1 • Tx naïve	*Group 1, Group 2, Group 3, Group 4*	*Stage 1* Four groups first stage for 28d	Outcomes • Change in circulating HCV RNA over first	Authors report significant relationships with

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	dose ranging study N= 64 *Group 1* n=16 *Group 2* n=18 *Group 3* n=15 *Group 4* n=14	• HCV RNA levels ≥10,000 IU/ml at screening • BMI 18 to 36 kg/m^2 <u>Exclusion</u> • Cirrhosis • Significant comorbidity • Positive for HBsAg, anti-HBc IgM Ab, or anti-HIV A	<u>Age</u> <u>mean (range)</u> 44.4 (23 to 57) 44.4 (30 to 57) 44.9 (29 to 62) 46.6 (27 to 62) <u>Male (%)</u> 11 (69%) 10 (56%) 11 (73%) 11 (19%) <u>Race n (%)</u> *White* 15 (94%) 16 (89%) 12 (80%) 14 (100%) *Other races not provided* <u>HCV -1a/1b (n/n)</u> 14/2 15/2 12/3	1. SOF 100 mg daily + PEG/RBV 2. SOF 200 mg daily + PEG/RBV 3. SOF 400 mg daily + PEG/RBV 4. Placebo + PEG/RBV **Stage 2** All pts continue with PEG/RBV alone for 44w Used response guided protocol & allowed early stopping Not all pts followed 48w <u>Follow-up</u> 24w post tx	28d • Rates of rapid virologic response (RVR = HCV RNA < limit of detection at week 4) • SVR 12 and 24 post tx • Viral breakthrough <u>Findings</u> **Change from baseline HCV RNA at Day 28** *Group 1* -5.3 log_{10}IU/ml *Group 2* -5.1 log_{10}IU/ml *Group 3* -5.3 log_{10}IU/ml	pharmaceutical companies Three authors are employed by and hold stock in Gilead Outcomes not reported for substantial minority of pts due to loss to follow-up and study withdrawal

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			10/4 Mean baseline HCV RNA (log_{10} IU/mL) (n) 6.64 6.28 6.49 6.48 IL28B genotype n (%) *CC* 4 (25%) 5 (28%) 4 (27%) 4 (29%) HOMA-IR ≤ 3 n (%) 10 (63%) 13 (72%) 7 (47%) 7 (50%) No/minimal fibrosis F0-1 n (%) 5 (31%)		*Group 4* -2.8 log_{10}IU/ml (*no p values provided*) **RVR at 28 days** *Group 1* 14 (88%) *Group 2* 17 (94%) *Group 3* 14 (93%) *Group 4* 3 (21%) (no p values provided) **SVR 12 post tx** n (%, 95% CI) *Group 1* 9 (56%, 30 to 80) *Group 2* 13 (72%, 47 to 90)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (33%) 5 (33%) 4 (29%) <u>Portal fibrosis – F1-2 n (%)</u> 11(69%) 10(56%) 9(60%) 9(64%) <u>Bridging fibrosis – F3 n (%)</u> 0 2(11%) 1(7%) 1(7%) <u>Loss to follow-up</u> Stage 1 1 pt Stage 2 16 pts		*Group 3* 13 (87%), 60 to 98) *Group 4* 7 (50%, 23 to 77) **SVR 24 post tx** n (%, 95% CI) *Group 1* 9 (56%, 30 to 80) *Group 2* 15 (83%, 59 to 96) *Group 3* 12 (80%, 52 to 96) *Group 4* 6 (43%, 18 to 71) **Viral breakthrough** *Phase I* No viral breakthrough *Phase II* 4 pts in Group 1; 2 pts in Group 3; 2	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					pts in Group 4 **Relapse** *Not reported* **Adverse Events** 54/63 pts reported "mild" or "moderate" AEs during 28d initial tx phase No pts discontinued therapy during 1st phase Most common AEs = fatigue, nausea, chills, headache, and arthralgia No difference between SOF groups and placebo group in 1st phase AEs	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					In 2nd phase, 5 serious AEs occurred > 50 days after ending SOF tx: peripheral ischemia, acute pancreatitis, anemia, depression, abdominal pain	
Non-published Studies Used in FDA Approval						
GS-US-334-0133 VALENCE study	Open-label N= 323 *Group 1 (genotype 2)* n=73 *Group 2 (genotype 3)* n=250 Trial originally planned as a randomized placebo-	Inclusion • Age > 18 • HCV genotype 2 or 3 • Tx naïve or tx experienced • HCV RNA levels ≥10,000 IU/ml at screening • Cirrhosis screening • Otherwise healthy • Contraception Exclusion • Hx of other significant chronic liver disease • Decompensated liver disease	*Group 1, Group 2;* Age mean (SD) 58 (10) 48 (10) Male (%) 40 (55%) 155 (62%) Race n (%) *White* 65 (89%) 236 (94%)	Intervention *Group 1* SOF 400mg/d and weight based RBV for 12w *Group 2* SOF 400 mg/d and weight based RBV for 24w Follow-up 24w post tx	Outcomes • SVR 12 post tx • Safety and tolerability Findings n (%) **Overall SVR 12 post tx** *Group 1* 68/73 (93%) *Group 2* 210/250 (84%)	Trial was on-going at time of FDA approval and results were preliminary. No final results have been published on clinicaltrials.gov or in the literature. Trial sponsored by Gilead. No

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	controlled trial with intervention group to receive SOF + RBV for 12 weeks. Altered in course to direct all genotype 3 pts to receive SOF + RBV for 24 w, and genotype 2 pts to SOF + RBV for 12 w; placebo group discontinued. Safety analysis includes discontinued pts – n = 419	• HIV, HBV, HCC, or other malignancy • Any condition, therapy or laboratory abnormality that might interfere with study • Chronic use of immunosuppressive agents or immunomoedulatory agents	*Black* 5 (7%) 0 (0%) *Asian* 1 (1%) 9 (4%) *Hispanic* 6 (8%) 36 (14%) Tx naïve 32 (44%) 105 (42%) Tx experienced 41 (56%) 145 (58%) *IFN Intolerant* 3 (4%) 10 (4%) *Non-Response* 10 (14%) 41 (16%)		**SVR 12 (Tx Naïve)** *Group 1* 31/32 (97%) *Group 2* 98/105 (93%) **SVR 12 (tx experienced)** *Group 1* 37/41 (90%) *Group 2* 112/145 (77%) **Overall relapse rate** *Group 1* 5/73 (7%) *Group 2* 32/249 (14%) **Relapse(tx naïve)** *Group 1* 1/32 (3%) *Group 2*	COI information available Study conducted in 10 countries in Europe

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Relapse/Breakthrough 28 (38%) 94 (38% <u>Baseline BMI (Kg/m^2)</u> <u>Mean (SD)</u> 26 (4) 25 (4) <u>Mean baseline HCV RNA (log_{10} IU/mL) (n)</u> 6.5 (0.7) 6.3 (0.7) <u>IL28B genotype n (%)</u> *CC* 24 (33%) 86 (34%) <u>Baseline cirrhosis</u> *No* 63 (86%) 192 (77%) *Yes* 10 (14%) 58 (23%0		5/105 (5%) **Relapse (tx experienced)** *Group 1* 4/41 (10%) *Group 2* 29/144 (20%) **Adverse events** N= 419 Group 1 (placebo) n=85 Group 2 (12wks) n=84 Group 3 (24 w) n=250 *Group 1, group 2, group 3* <u>Any AE n (%)</u> 61 (72%) 72 (86%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Baseline ALT *≤ 1.5 x ULN* 39 (53%) 64 (26%) *1.5 x ULN* 34 (47%) 186 (74% Lost to follow-up 0 1 (< 1%)		228 (91%) Common AEs Fatigue, headache, pruritus, asthenia, insomnia, nasopharyngitis, nausea, dry skin, diarrhea, dyspnea, cough, irritability Serious AE n (%) *Group 1* 2 (2.4%) one each of adenocarcinoma of colon, gastroenteritis *Group 2* 0 *Group 3* 10 (4%), one each of: arrhythmia, haemorrhoidal haemorrhage, biliary colic, road	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					traffic accident, amylase increased, lipase increased, hyperglyacemia, HCC, invasive ductal breast carcinoma, complex regional pain syndrome, suicide attempt <u>Grade 3 or 4 AE</u> 4 (5%) 3 (4%) 17 (7%)	
GS-US-334-0123 PHOTON-1 study	Open label study N= 223 N for efficacy analysis = 210 (13 group 2 pts had not completed trial at FDA review)	<u>Inclusion</u> • Age ≥ 18 • HCV genotype 1, 2 or 3 • HIV-1 infection • HCV RNA levels ≥10,000 IU/ml at screening • Cirrhosis screening • HIV antiretroviral therapy (ARV) criteria: o ARV untreated, CD4 T-cell count > 500	*Group 1, Group 2, Group 3* <u>Age</u> <u>mean (SD)</u> 49 (10) 54 (6) 48 (8) <u>Male (%)</u> 55 (81%) 37 (90%)	<u>Intervention</u> *Group 1* SOF 400mg/d and weight based RBV for 12w *Group 2* SOF 400 mg/d and weight based RBV for	<u>Outcomes</u> • SVR 12 post tx • Safety and tolerability <u>Findings</u> *Group 1, Group 2, Group 3* **Overall SVR 12 Post Tx** **n (%, 95% CI)**	Trial not completed at FDA review. 13 pts in group 2 not included in efficacy data set.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	Group 1 (genotype 2/3 tx naive) n=68 *Group 2 (genotype 2/3 tx experienced)* n=28 (completed trial, 41 enrolled in group) *Group 3 (genotype 1 tx naïve)* n=114	cells/mm3 o Stable, protocol approved ARV regimen > 8 w, CD4 T-cell count > 200 cells/mm2, undetectable plasma HIV-1 RNA level for ≥ 8 w • Approved ARV regimen • No investigational drug use within 30 days • Otherwise healthy • Contraception <u>Exclusion</u> • Prior tx for genotype 1 pts • Other chronic liver disease • Decompensated liver disease • HBV • Hx solid organ transplant • Contradiction to RBV tx • Serious infection requiring parenteral antibiotics, antivirals or antifungals within 30 days • Chronic use of	93 (82%) <u>Race n (%)</u> *White* 52 (76%) 32 (78%) 69 (61%) *Black* 8 (12%) 7 (17%) 37 (32%) *Asian* 1 (1%) 1 (2%) 6 (5%) *Hispanic* 19 (28%) 10 (24%) 25 (22%) <u>HCV genotype</u> *HCV-1a* 0 0	24w *Group 3* SOF 400 mg/d and weight based RBV for 24w <u>Comparator</u> *None* <u>Follow-up</u> 24w post tx	51/68 (75, 63-85) 26/28 (93, 77-99) 87/114 (76, 67-84) **SVR 12 Genotype HCV-1a** *(Group 3)* 74/90 (82, 73-89) **SVR 12 Genotype HCV-1b** *(Group 3)* 13/24 (54, 33-74) **SVR 12 Genotype HCV-2** *(Group1, Group 2)* 23/26 (88, 70-98) 14/15 (93, 68-99.8) **SVR 12 Genotype HCV-3** *(Group 1, Group2)* 28/42 (67, 50-80) 12/13 (92, 64-99.8) **Overall Relapse Rate n (%)** 12/67 (18%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		immunosuppressive agents or immunomoedulatory agents	90 (79%) *HCV-1b* 0 0 24 (21%) *HCV-2* 26 (38%) 24 (59%) 0 *HCV-3* 42 (62%) 17 (41%) 0 <u>Group 2 Tx experienced</u> *IFN intolerant* 9 (22%) *Partial/null-response* 7 (17%) *Relapse/Breakthrough* 25 (61%)		2/28 (7%) 25/113 (22%) **Adverse Events (Safety Analysis n=223)** *Group 1, Group 2, Group 3* <u>Any AE n (%)</u> 57 (84%) 37 (90%) 106 (93%) <u>Common AEs</u> Fatigue, insomnia, nausea, headache, upper respiratory tract infection, diarrhea, irritability anemia, cough, dizziness <u>Serious AE n (%)</u> *Group 1* 5 pts (7.4%), 14 events - one each	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Cirrhosis *No* 61 (90%) 31 (76%) 109 (96%) *Yes* 7 (10%) 10 (24%) 5 (4%) Baseline BMI (Kg/m^2) mean (SD) 27 (4) 27 (5) 27 (5) Mean baseline HCV RNA *< 6 log_{10} IU/mL* 21 (31%) 7 (17%) 22 (19%) *≥ 6 log_{10} IU/mL* 47 (69%) 34 (83%)		of acute MI, pneumonia, incision site infection, septic shock, staphylococcal bacteremia, intentional overdose, fracture, encephalopathy, completed suicide, drug abuse, suicide attempt, acute renal failure, pulmonary embolism, respiratory failure *Group 2* 1 pt (2.4%), 3 events: pneumonia, COPD, leukocytoclastic vasculitis	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			92 (81%) <u>IL28B genotype n (%)</u> *CC* 25 (37%) 20 (49%) 30 (26%) *CT* 37 (54%) 17 (41%) 57 (50%) *TT* 6 (9%) 4 (10%) 26 (23%) <u>ARV Tx at Enrollment</u> *No* 7 (10%) 2 (5%) 2 (2%) <u>Baseline HIV-1 RNA</u> *< 50 copies/mL* 60 (88%)		*Group 3* 8 pts (7%), 18 events: one each (unless noted) of anemia, leukocytosis, atrial fibrillation, atrial flutter, abdominal pain, colitis, enteritis, chest pain, cellulitis (2), gastroenteritis salmonella, respiratory tract infection, intentional overdose, diabetic ketoacidosis, altered state of consciousness, bi-polar disorder, acute renal failure (2) <u>Grade 3 or 4 AE</u> 7 (10.3%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			40 (98%) 108 (95%) *≥ 50 copies/mL* 8 (12%) 1 (2%) 6 (5%) Baseline CD4 (cells/mm^3)[3] mean (SD) 585 (246) 658 (333) 636 (251) Lost to follow-up 5 (7%) 1 (2%) 1 (2%)		3 (7.3%) 15 (3.2%)	
P7977-2025 Pre-transplant study	Open-label trial On-going N=61 (protocol on clinical trials.gov states 50, FDA analysis	Inclusion • Age ≥ 18 years • Patients meeting the MILAN criteria for liver transplantation for HCC secondary to HCV with a MELD < 22 and a HCC weighted MELD of ≥ 22	Status of pts at time of FDA analysis (n=61) n (%) In tx/pre transplant 9 (14.8%) Had liver transplant while on tx	Intervention SOF 400mg/d and weight based RBV for up to 48 weeks prior to transplantation or until	Outcomes • Post transplant reinfection as defined by SVR at 12 w post transplant (pTVR12) and 24 w post	Trial is not completed. FDA presentation of data is incomplete, does not include n's for

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	reports 61 patients received at least one dose of drug) Study was originally designed to test SOF + RBV for 24 w prior to transplant. FDA reports that 11/15 pts (73%) who completed 24 w tx relapsed in the pre-transplant phase, so tx time was extended to 48w for pts who had not been transplanted	• Child-Pugh Score ≤ 7 • HCV RNA levels ≥10,000 IU/ml at screening • No investigational drug use within 30 days • Contraception <u>Exclusion</u> • Pregnant, nursing, pregnant partner • Other chronic liver disease • Post transplant immunosuppressive regimen not consistent with protocol • Decompensated cirrhosis • HBV • Hx or previous solid organ transplant • Evidence of renal impairment • Hx or current psychiatric illness, immunologic disorder, hemoglobinopathy, pulmonary or cardiac	29 (47.5%) Completed 24 w tx and then had transplant 8 (13.1%) Completed 24 w tx and terminated from trial due to disease progression 2 (3.3%) Completed 24 w tx, relapsed in post tx and currently being tx again in re-tx sub-study 7 (11.5%) Prematurely discontinued tx 6 (9.8%) for • Adverse event 2 (3.3%) • Efficacy failure	transplantation <u>Mean exposure to SOF+RBV prior to transplantation</u> 17.7 w (no n) <u>Follow-up</u> 48 w post transplant	transplant (pTVR24) • SVR 12 w post treatment • Safety and tolerability <u>Findings n (%)</u> **Virological response** 41 pts who had tx underwent transplant. Only 38 of those had HCV RNA < LLOQ at time of transplantation and were considered for further analysis. One of those 38 pts was transplanted with an HCV infected liver and excluded from analysis. Of the 37	many measures and does not provide clear information on tx failure/relapse. FDA reviewer notes that study population limited to patients with HCV related HCC and may not be applicable to all transplant candidates.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		disease, porphyria, poorly controlled diabetes, cancer other than HCC, acute pancreatitis • Hx of receiving systemic antineoplastic or immunomodulatory treatment (including radiation) w/I 6 months • Tx with transcatheter arterial chemoembolization (TACE) or radio frequency ablation (RFA) w/I 30 days • Participation in a clinical trial w/i 3 months • Contradiction to RBV tx • Chronic use of immunosuppressive agents prior to tx	4 (6.6%) Age mean (range) 59 (46 to 73) Male (%) 80.3% (*no n reported*) Race n (%) *White* 90.2% (*no n reported*) HCV genotype *HCV-1a* 39.3% (*no n reported*) *HCV-1b* 34.4% (*no n reported*) *HCV-2* 13.1% (*no n reported*) *HCV-3* 11.5% (*no n reported*) *HCV-4* 1.6% (*no n reported*)		included patients, 35 had been followed to 12 w post transplant and 24 patients to 24 w post transplant. Post-transplant virological response n (%, 95% CI) **pTVR 12** 23/35 (65.7, 50.4-78.9) **pTVR 24** 17/24 (70.8, 52.1-85.4) ***Inadequate information to identify relapse rates*** **Adverse Events** (n=61 for safety	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Tx experienced *75.4%* (*no n reported*) Mean baseline HCV RNA *≥ 6 log_{10} IU/mL* 67.2% (*no n reported*) IL28B genotype n (%) *Non-CC* 78.3% (*no n reported*) ARV tx at enrollment *No* 7 (10%) 2 (5%) 2 (2%) Baseline Child-Pugh Turcotte Score *5* 42.6% (no n) *6* 29.5% (no n) *7*		analysis) Any adverse event 52/61 (85.2%) Common AEs Fatigue (36.1%), anemia (23.0%), headache (21.3%) Significant AEs 11/61 (18%), not considered related to study drug Grade 4 laboratory abnormality 6 (9.8%) • Decreased lymphocyte count 4 (6.6%) • Increased aspartate aminotransferase 1 (1.6%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			23.0% (no n) *8* 4.9% (no n) <u>Baseline MELD Score = 7 or 8</u> 49.2%		• Total bilirubin 1 (1.6%) <u>Grade 3 laboratory abnormality</u> 21 (31.4%) • Decreased hemoglobin 9 (14.8%) • Increased non-fasting glucose 7 (11.5%) • Increased total bilirubin 5 (8.2%)	
Non-published Study on Sofosbuvir and Simeprevir Combination Treatment						
COSMOS trial NCT01466790 Completed January 2014 ***Preliminary results***	Randomized open-label trial N=167 (in published abstract; n=168 in clinical trials.gov)	<u>Inclusion</u> • Age 18 to 70 • HCV genotype 1 • HCV RNA levels ≥10,000 IU/ml at screening • Cohort inclusion: o Cohort 1: previous tx with PEG+RBV for at least 12 w with a null response and	*No patient characteristic information available*	<u>Intervention</u> Divided into two cohorts, enrolled sequentially, and each cohort divided into four groups.	<u>Outcomes</u> • SVR 12 post tx • Safety and tolerability ***<u>NOTE:</u> The published abstract only reports SVR12 data on***	VERY small N Allocation to treatment weighted such that nearly twice as many subjects received SOF + SME + RBV as

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
presented at the American Association for the Study of Liver Diseased Conference and abstract published in *Hepatology* December, 2013. (Jacobson 2013b) full article not available.	<u>Cohort 1</u> *Group 1* n=14 *Group 2* n=27 *Group 3* n=15 *Group 4* n=24 <u>Cohort 2</u> *Group 1* n=14 *Group 2* n=27 *Group 3* n=16 *Group 4* n=30	Metavir score F0-F2 o Cohort 2: Tx naïve or previous tx with PEG+RBV for at least 12 w with a null response and Meativr score F3-F4 o Null response defined as < 2log10 IU/mL reduction in HCV RNA from baseline at week 12 of tx • Liver biopsy • Contraception <u>Exclusion</u> • Hepatic decompensation • Other significant liver disease • HIV, HBV, or non-genotype 1 HCV • Hx of malignancy w/I 5 yrs		*Group 1* SOF 400 mg/d + simeprevir (SME) 150 mg/d for 12 w *Group 2* SOF 400 mg/d + simeprevir (SME) 150 mg/d + weight based RBV for 12 w *Group 3* SOF 400 mg/d + simeprevir (SME) 150 mg/d for 24 w *Group 4* SOF 400 mg/d + simeprevir (SME) 150 mg/d + weight based RBV for	***Cohort 1*** ***The total number of patients reported on who received SOF + SME alone = 28*** <u>Findings n (%)</u> **SVR 12 – Cohort 1** *Group 1* 13/14 (92.9%) *Group 2* 26/27 (96.3%) *Group 3* 14/14 (100%) *Group 4* 19/24 (79.2%)	SOR + SME alone.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
				24 w <u>Follow-up</u> 24 w post tx		

Abbreviations

AAT – alpha1-antitrypsin; AEs – adverse events; ALT =Alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index; d – day; ECG – electrocardiogram; eRVR – extended rapid virologic response; f/u – follow-up; HAI = histology activity index; Hb – hemoglobin; HbA1c – glycated hemoglobin; HBV – hepatitis B virus; HCV – hepatitis C virus; HCV-1 – HCV genotype 1 (and equivalents for genotypes 2, 3, 4, 5, 6);HIV – human immunodeficiency virus; HOMA-IR – homeostasis model assessment of insulin resistance; Hx – history; INF – interferon; INR – international normalized ratio; m – months; mg – milligrams; pt – patient; PEG – pegalated interferon alpha; pTVR – post-transplant virological response; rec'd – received; RNA – ribonucleic acid; RBV – ribavirin; RCT – randomized controlled trial; RVR = rapid virologic response or HCV RNA below levels of detection; SOF – sofosbuvir; tx – treatment; SVR – sustained virologic response; ULN – upper limit of normal; w – weeks; w/I – within; w/o – without

Appendix D. Critical Appraisal Summary

Table 1. Internal Validity (Risk of Bias) Criteria

Author, Year (Trial)	Internal Validity (Risk of Bias) Criteria											
	Randomization adequate?	Allocation concealment adequate?	Groups comparable at baseline?	Masking of investigator to treatment assignment?	Masking of treatment team to treatment assignment?	Masking of patient to treatment assignment?	All treatment groups received same care aside from intervention(s)?	Appropriate length of follow-up? (follow-up length)	Groups followed for equal amount of time or analysis adjusted for time?	Intention to treat analysis performed or possible with data provided?	Outcomes measured in valid and reliable way?	Outcome assessors masked to treatment assignment?
Gane, 2013 (ELECTRON)	U	U-NR	N	N	N	N	U-NR	Y (≥ 24w)	Y	Y	Y	N
Jacobson, 2013a (Study 1) (POSITRON)	U	U-NR	Y	U	U	U	U	N (12w)	Y	Y (modified)	Y	U
Jacobson, 2013a (Study 2) (FUSION)	U	U-NR	Y	U	U	U	U-NR	N (12w)	Y	Y (modified)	Y	U
Kowdley, 2013 (ATOMIC)	N	Y	N	N	N	N	U-NR	Y (≥ 24w)	Y	Y (modified)	Y	N
Lawitz, 2013 (Lancet) (Study 1)	Y (Cohort A)	Y (Cohort A)	U (Cohort A)	Y (Cohort A to 12 w)	U-NR	Y (Cohort A to 12 w)	U	Y (≥ 24w)	Y	Y	Y	U-NR

Author, Year (Trial)	Internal Validity (Risk of Bias) Criteria											
	Randomization adequate?	Allocation concealment adequate?	Groups comparable at baseline?	Masking of investigator to treatment assignment?	Masking of treatment team to treatment assignment?	Masking of patient to treatment assignment?	All treatment groups received same care aside from intervention(s)?	Appropriate length of follow-up? (follow-up length)	Groups followed for equal amount of time or analysis adjusted for time?	Intention to treat analysis performed or possible with data provided?	Outcomes measured in valid and reliable way?	Outcome assessors masked to treatment assignment?
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	N	NA	NA	N	N	N	NA	N (12w)	NA	NA	Y	N
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	U	U-NR	Y	N	N	N	U-NR	Y (≥ 24w)	Y	U	Y	N
Osinusi, 2013 (Study 1)	NA	NA	NA	N	N	N	NA	Y (≥ 24w)	NA	NA	Y	N
Osinusi, 2013 (Study 2)	U	U-NR	U	N	N	N	U-NR	Y (≥ 24w)	Y	Y	Y	N
Rodriguez-Torres, 2013	Y	U-NR	U	Y	U	Y	Y	Y (≥ 24w)	N	N	Y	U

Key: Y – Yes; N – No; U – Unclear; NA – Not applicable; NR – Not reported

Table 2. External Validity (Risk of Bias) Criteria

Author, Year (Trial)	External Validity (Applicability) Criteria					
	Study reports on important end outcomes? (or adequate rationale if surrogate used)	Single primary outcome used? (or adequate rationale if composite outcome used)	Author(s) have financial or other substantive conflicts of interest?	Sponsor(s) have financial or other substantive conflicts of interest?	Study population similar to population to whom intervention will be applied?	Control group received standard of care (adequate comparator)?
Gane, 2013 (ELECTRON)	Y (SVR 24)	Y	Y	Y	U (no HCV-1 enrolled)	N (HCV-1; various regimens with SOF + RBV, but no PEG, bocep or telap) N (HCV-2,3; various regimens & duration of SOF +/- RBV +/- PEG, but all grps rec'd SOF)
Jacobson, 2013a (Study 1) (POSITRON)	N (SVR 12)	Y	Y	Y	U (no HCV-1 enrolled)	N (placebo)
Jacobson, 2013a (study 2) (FUSION)	N (SVR 12)	Y	Y	Y	U (no HCV-1 enrolled)	N (HCV 2,3 w/o PEG)
Kowdley, 2013 (ATOMIC)	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled)	N (HCV-1 w/o bocep or telap)
Lawitz, 2013 (Lancet)	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled in RCT portion)	N (HCV-1 w/o bocep or telap)

Author, Year (Trial)	External Validity (Applicability) Criteria					
	Study reports on important end outcomes? (or adequate rationale if surrogate used)	Single primary outcome used? (or adequate rationale if composite outcome used)	Author(s) have financial or other substantive conflicts of interest?	Sponsor(s) have financial or other substantive conflicts of interest?	Study population similar to population to whom intervention will be applied?	Control group received standard of care (adequate comparator)?
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	N (SVR 12)	Y	Y	Y	U (largely HCV-1)	NA
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	N (SVR 12)	Y	Y	Y	U (HCV-2,3)	Y (HCV-2,3 24w RBV + PEG)
Osinusi, 2013 (Study 1)	Y (SVR 24)	Y	Y	N	U (HCV-1 w/unfavorable characteristics)	NA
Osinusi, 2013 (Study 2)	Y (SVR 24)	Y	Y	N	U (HCV-1 w/unfavorable characteristics)	N (RBV 600mg rather than 1000 or 1200mg)
Rodriguez-Torres, 2013	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled)	N (HCV-1 w/o bocep or telap)

Key: Y – Yes; N – No; U – Unclear; NA – Not applicable

Abbreviations: bocep – boceprivir; grps – groups; HCV – hepatitis C virus; PEG – pegalated interferon alpha; RBV – ribavirin; SVR – sustained virologic response; telap – telaprevir

Table 3. Overall Quality Summary

Overall Quality Summary				
Author, Year (Trial)	**How well was the study done to minimize bias in study design? (Good, Fair, Poor)**	**How well did the study respond to the PICO of this report? (Good, Fair, Poor)**	**Overall Study Quality (Good, Fair, Poor)**	**Comments**
Gane, 2013 (ELECTRON)	Poor	Poor	**Poor**	Open label study; largely a PEG regimen ranging study for HCV-2,3 and PEG-sparing for HCV-1
Jacobson, 2013a (Study 1) (POSITRON)	Poor	Poor	**Poor**	Placebo control RCT; interferon treatment contraindicated, unacceptable or prior discontinuation due to unacceptable AEs
Jacobson, 2013a (Study 2) (FUSION)	Poor	Poor	**Poor**	Active control RCT; no response to prior interferon containing regimen; duration ranging length of RBV tx (12w vs 16w)
Kowdley, 2013 (ATOMIC)	Poor	Poor	**Poor**	Open label study; duration ranging 12w vs 24w PEG + RBV
Lawitz, 2013 (Lancet)	Poor	Poor	**Poor**	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	Poor	Poor	**Poor**	Open label, single group study; tx naïve; 89% HCV-1 (11% HCV-4, 5, 6); 17% cirrhotic
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	Poor	Poor	**Poor**	Open label non-inferiority RCT; tx naïve; HCV-2, 3; 20% cirrhotic

Overall Quality Summary				
Author, Year (Trial)	How well was the study done to minimize bias in study design? (Good, Fair, Poor)	How well did the study respond to the PICO of this report? (Good, Fair, Poor)	Overall Study Quality (Good, Fair, Poor)	Comments
Osinusi, 2013 (Study 1)	Poor	Poor	**Poor**	Proof of concept study (n=10) with HCV-1 and unfavorable tx characteristics
Osinusi, 2013 (Study 2)	Poor	Fair	**Poor**	Open label RCT with HCV-1 and unfavorable tx characteristics
Rodriguez-Torres, 2013	Poor	Poor	**Poor**	Open label RCT; tx naïve; with HCV-1; dose ranging

Abbreviations: AEs – adverse events; HCV – hepatitis C virus; HCV-1 – HCV genotype 1 (and equivalents for genotypes 2, 3, 4, 5, 6); mg – milligrams; PEG – pegalated interferon alpha; RBV – ribavirin; RCT – randomized controlled trial; rec'd – received; tx – treatment; w – weeks

Definitions Used for Domains with Unique Features for Condition

Masking: If study was open label did not consider masking/blinding adequate for investigators, clinicians, patients or outcome assessors

Length of follow-up: Considered inadequate if greater than 24 weeks post-treatment

Important outcomes/surrogates: Accepted any important clinical outcomes such as development of end-state liver disease and considered SVR 24 to represent an adequate surrogate measure because strongly linked to clinical outcomes; considered inadequate if measure reported was SVR 12.

Comparability of study population to likely use population: Rated as uncertain if study restricted population to those likely to need treatment in real world situations, including representative populations of those with poor prognostic factors such as male sex, black race, and cirrhosis or advanced hepatic fibrosis, as well as those who are HBV or HIV positive, actively misusing alcohol and other drugs, and those who are unable to use interferon.

Standard of care: Current standard of care regimen for HCV-1 includes triple therapy with PEG, RBV, and a polymerase inhibitor (boceprevir or telaprevir) using response guided therapy; for HCV-2 or -3 standard of care is 24 weeks of treatment with PEG and RBV.

Appendix E: Private Payer Policies

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Pharmacy Clinical Policy Bulletins
Aetna Non-Medicare Prescription Drug Plan

Subject: Hepatitis C

Status	Drug	PR	PR-QL	PR-AL	ST	M EX‡
P	*ribavirin*					
P	**Incivek™** *(telaprevir)*	X	X			
P	**Intron-A ®** *(interferon alfa-2b)*	X				
P	**Peg-Intron ®** *(peginterferon alfa-2b)*	X				
P	**Peg-Intron Redipen/pak ®** *(peginterferon alfa-2b)*	X				
P	**Pegasys ®** *(peginterferon alfa-2a)*	X				
NP	**Infergen ®** *(interferon alfacon-1)*	X				
NP	**Victrelis™** *(boceprevir)*	X	X			
FE	**Olysio™** *(simeprevir)*	X	X			X
FE	**Sovaldi™** *(sofosbuvir)*	X	X			X

Note: Note: Precertification review for Incivek, Infergen, Intron-A, Olysio, Peg-Intron, Pegasys, Sovaldi,and Victrelis are handled through Aetna Specialty Precert Unit

Refer to Medical CPB 400 http://aetnet.aetna.com/mpa/cpb/400_499/0404.html for precertification criteria for these drugs.

Additional Information

› Clinical Policy Bulletin Notes

*P = Preferred
FE = Formulary Excluded
NP = Nonpreferred
PR = Precertification
QL = Quantity Limits
AL = Age Limits
ST = Step-Therapy
‡M EX = Medical Exception
+RxStep=Rx Step
^ETM=Essential Therapy Management

*The lists above are subject to change. Not all programs - for example step-therapy, precertification, and quantity limits - are available in all service areas.

Policy:

I. Precertification Criteria

Under some plans, including plans that use an open or closed formulary, **Incivek, Infergen, Intron-A, Olysio, Pegasys, Peg-Intron/ Redipen/pak, Sovaldi,** and **Victrelis** are subject to precertification. If precertification requirements apply Aetna considers these medications to be medically necessary for those members who meet all of the following precertification criteria:

For **Sovaldi**

(In order to be eligible for the max time of approval, members must meet both intial and reauthorization criteria.)

<u>For initial authorizaion:</u>

- A documented diagnosis of one of the following:
  - Chronic Hepatits C Virus (HCV) infection, genotype 1, **AND**
    - Concurrent therapy with *peginterferon alfa* (PEG) and *ribavirin* (RBV) (Max Time of Approval 12 weeks)
  - HCV infection, genotype 1, PEG-ineligible patient*, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks); **OR**
    - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
  - HCV infection, genotype 1, PEG/ RBV (without HCV protease inhibitor (PI)) nonresponder patients, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks)
  - HCV or HCV/ HIV infection, genotype 1, PEG/ RBV (with or without HCV (protease inhibitor) PI) nonresponder patients, **AND**
    - Concurrent therapy with PEG and RBV (Max Time of Approval 12 to 24 weeks, 12 weeks for Sovaldi only.)
  - HCV/ HIV coinfected patients, genotype 1, treatment naive or prior nonresponder, **AND**
    - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)

- HCV/ HIV coinfected patients, genotype 1, treatment naive or prior nonresponder, PEG-ineligible patient*, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 1, post-liver transplant, **AND**
  - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 to 24 weeks); **OR**
  - Concurrent therapy with RBV with or without PEG (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 2, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 2, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 12 weeks (16 weeks in cirrhosis)); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 2 or 3, post-liver transplant, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 3, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 3, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 4, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 4, PEG-ineligible patients*, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV infection, genotype 4, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks); **OR**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 5 or 6, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 5 or 6, PEG/ RBV nonresponder, **AND**

        - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
    - HCV infection, in decompensated cirrhosis or in patient with documented hepatocellular carcinoma (HCC) awaiting liver transplantation, **AND**
        - Concurrent therapy with RBV (Max Time of Approval 48 weeks or until liver transplantation)

<u>For reauthorization at 8 weeks:</u>

- Initial authorization criteria above has been met **AND**
    - HCV RNA levels have declined > 2 $\log_{10}$ IU/ mL at 4 weeks of therapy

*Interferon ineligible is defined as meeting one or more of the following criteria:

- Uncontrolled seizures
- Suicidal attempt within past year
- Moderate to severe retinopathy
- Neutrophils <750 cells/ mm^3, results within the past month
- Hemoglobin <10 g/ dL, results within the past month
- Platelets <50 000 cells/ mm^3, results within the past month
- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, COPD
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV
- Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens-Johnson syndrome to alpha interferons, or any of its components
- Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
- Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before treatment

According to the manufacturer, **Incivek, Olysio, Sovaldi,** and **Victrelis** can be dosed up to a maximum daily dose indicated in the table below. A quantity of these drugs will be considered medically necessary as indicated below:

Drug	Maximum Daily Dose	Dosage Strength	Quantity Limits
Incivek	2250 mg	375 mg	Up to 180 tablets in days
Olysio	150 mg	150 mg	Up to 30 capsules i days
Sovaldi	400 mg	400 mg	Up to 30 tablets in 3 days
Victrelis	2400 mg	200 mg	Up to 360 tablets in days

II. Medical Exception Criteria

Olysio and **Sovaldi** are currently listed on the Aetna Formulary Exclusions list. Therefore, they are excluded from coverage for members enrolled in a prescription drug benefit plan that uses a closed formulary unless a medical exception is granted. Aetna considers these medications to be medically necessary for those members who meet the following criteria:

For **Olysio**

(In order to be eligible for the max time of approval, members must meet both intial and reauthorization criteria.)

<u>For initial authorizaion:</u>

- A documented diagnosis of one of the following:
  - Chronic Hepatits C Virus (HCV) infection or HCV/ HIV coinfection, genotype 1, **AND** all of

the following:

- Concurrent therapy with *peginterferon alfa* (PEG) and *ribavirin* (RBV) (Max Time of Approval 24 weeks. Olysio approval for 12 weeks.)
- If HCV genotype 1a, NS3 Q80K polymorphism is not detected prior to treatment
- Patient has not failed previous therapy with a treatment regimen that includes HCV protease inhibitors (i.e., Incivek, Olysio, Victrelis)

- HCV infection or HCV/ HIV coinfection, genotype 1, PEG/ RBV (without HCV protease inhibitor (PI)) nonresponder patients, **AND** all of the following:
  - Concurrent therapy with PEG and RBV (Max Time of Approval 48 weeks. Olysio approval for 12 weeks.)
  - If HCV genotype 1a, NS3 Q80K polymorphism is not detected prior to treatment
  - Patient has not failed previous therapy with a treatment regimen that includes HCV protease inhibitors (i.e., Incivek, Olysio, Victrelis)
- HCV infection, genotype 1, PEG-ineligible patient* **AND** all of the following:
  - Concurrent therapy with Sovaldi with or without RBV (Max Time of Approval 12 weeks.)
- HCV infection, genotype 1, post-liver transplant **AND** all of the following:
  - Concurrent therapy with Sovaldi with or without RBV (Max Time of Approval 12 to 24 weeks.)
- HCV infection, genotype 4, **AND** all of the following:
  - Concurrent therapy with PEG and RBV (Max Time of Approval 24 to 48 weeks. Olysio approval for 12 weeks.)
  - Patient has not failed previous therapy with a treatment regimen that includes HCV protease inhibitors (i.e., Incivek, Olysio, Victrelis)

<u>For reauthorization at 8 weeks:</u>

- Initial authorization criteria above has been met **AND**
  - HCV RNA levels are < 25 IU/ mL at 4 weeks of therapy

For **Sovaldi**

(In order to be eligible for the max time of approval, members must meet both intial and reauthorization criteria.)

<u>For initial authorizaion:</u>

- A documented diagnosis of one of the following:
  - Chronic Hepatits C Virus (HCV) infection, genotype 1, **AND**
    - Concurrent therapy with *peginterferon alfa* (PEG) and *ribavirin* (RBV) (Max Time of Approval 12 weeks)
  - HCV infection, genotype 1, PEG-ineligible patient*, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks); **OR**
    - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
  - HCV infection, genotype 1, PEG/ RBV (without HCV protease inhibitor (PI)) nonresponder patients, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks)
  - HCV or HCV/ HIV infection, genotype 1, PEG/ RBV (with or without HCV (protease inhibitor) PI) nonresponder patients, **AND**
    - Concurrent therapy with PEG and RBV (Max Time of Approval 12 to 24 weeks, 12 weeks for Sovaldi only.)
  - HCV/ HIV coinfected patients, genotype 1, treatment naive or prior nonresponder, **AND**
    - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
  - HCV/ HIV coinfected patients, genotype 1, treatment naive or prior nonresponder, PEG-ineligible patient*, **AND**
    - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks)
  - HCV infection, genotype 1, post-liver transplant, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 to 24 weeks); **OR**
    - Concurrent therapy with RBV with or without PEG (Max Time of Approval 24

weeks)

- HCV or HCV/ HIV infection, genotype 2, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 2, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 12 weeks (16 weeks in cirrhosis)); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 2 or 3, post-liver transplant, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 3, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 3, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 4, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 4, PEG-ineligible patients*, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV infection, genotype 4, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks); **OR**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 5 or 6, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 5 or 6, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, in decompensated cirrhosis or in patient with documented hepatocellular carcinoma (HCC) awaiting liver transplantation, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 48 weeks or until liver transplantation)

For reauthorization at 8 weeks:

- Initial authorization criteria above has been met **AND**
  - HCV RNA levels have declined > 2 $\log_{10}$ IU/ mL at 4 weeks of therapy

*Interferon ineligible is defined as meeting one or more of the following criteria:

- Uncontrolled seizures
- Suicidal attempt within past year
- Moderate to severe retinopathy
- Neutrophils <750 cells/ mm^3, results within the past month
- Hemoglobin <10 g/ dL, results within the past month
- Platelets <50 000 cells/ mm^3, results within the past month
- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, COPD
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV
- Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens-Johnson syndrome to alpha interferons, or any of its components
- Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
- Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before treatment

Special Notes:

Place of Service:
Outpatient

The above policy is based on the following references:

1. AHFS Drug Information® with AHFSfirstReleases®. (www.statref.com), American Society Of Health-System Pharmacists®, Bethesda, MD. Updated periodically.
2. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.
3. Drug Facts and Comparisons on-line. (www.drugfacts.com), Wolters Kluwer Health, St. Louis, MO. Updated periodically.
4. PDR® Electronic Library™ [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.
5. Clinical Pharmacology [Internet database]. Gold Standard Inc. Tampa, FL. Updated periodically.
6. Olysio™ [package insert]. Titusville, NJ: Janssen Products, LP; November 2013.
7. Sovaldi™ [package insert]. Foster City, CA: Gilead Sciences, Inc.; December 2013
8. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America: Recommendations for Testing, Managing, and Treating Hepatitis C. http://www.hcvguidelines.org/full-report-view [retrieved on 01/29/2014]

March 5, 2014

Medication	Quantity Limit
Sovaldi (sofosbuvir)	1 tablet per day

OVERRIDE(S)
Prior Authorization of Benefits

APPROVAL DURATION
Based on Genotype or hepatocellular carcinoma status:

Status type (HCV Mono-infected or HCV/HIV-1 Co-infected)	Total Approval Duration
Genotype 1 or 4 CHC	12 weeks
Genotype 1 CHC ineligible for an interferon-based regimen	24 weeks
Genotype 2 CHC	12 weeks
Genotype 3 CHC	24 weeks
Hepatocellular Carcinoma awaiting liver transplant	Up to 48 weeks*

* Therapy duration is recommended for up to 48 weeks or until the time of liver transplantation, whichever occurs first.

APPROVAL CRITERIA

Requests for Sovaldi (sofosbuvir) may be approved if the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Documentation is provided for a diagnosis of chronic hepatitis C (CHC) infection; **AND**
III. Individual has compensated liver disease (including cirrhosis); **AND**
IV. Individual is using with one of the following antiviral treatment regimens:
    a. In combination with peg interferon and ribavirin for the following:
        1. Individuals with hepatitis C virus (HCV) Genotype 1; **OR**
        2. Individuals with HCV Genotype 4;

    OR
    b. In combination with ribavirin alone for the following:
        1. Individuals with HCV Genotype 1 that are ineligible for an interferon-based regimen, as defined by the presence of **one** of the following:
            A. Autoimmune hepatitis; **OR**
            B. Child-Pugh score greater than 6 (Class B or C) before or during interferon treatment; **OR**
            C. Known hypersensitivity to interferon products; **OR**
        2. Individuals with HCV Genotype 2; **OR**
        3. Individuals with HCV Genotype 3; **OR**
        4. Individuals with CHC and concurrent hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation).

Requests for concomitant use of two or more of the following; Incivek (telaprevir), Victrelis (boceprevir), Olysio (simeprevir), or Sovaldi (sofosbuvir) will not be approved.

Child Pugh Classification

Parameters			
Points Assigned	1 point	2 points	3 points
Encephalopathy	None	Minimal	Advanced coma
Ascites	None	Easily controlled	Poorly controlled
Serum Bilirubin	<2mg/dL	2-3 mg/dL	>3 mg/dL
Serum Albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
INR	INR <1.7	INR 1.7-2.3	INR >2.3

Child Pugh Score Interpretation

Class A	5-6 points	Well compensated liver disease
Class B	7-9 points	Significant functional compromise
Class C	10-15 points	Uncompensated liver disease

Sovaldi
(sofosbuvir)

SOVALDI with RIBAVIRIN

Sovaldi (sofosbuvir) RIBAVIRIN
(Copegus, Rebetol, Ribapak, Ribasphere, Ribatabs, ribavirin - all strengths)

Pre - PA Allowance
None

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

Chronic Hepatitis C

AND ONE of the following:

1. Genotype 1

   AND ONE of the following:
   a. Interferon ineligible, intolerant, or unwilling

2. Genotype 2 or 3

3. Genotype 1, 2, 3, or 4

   AND MUST have the following:
   a. Hepatic carcinoma(s) awaiting liver transplantation
      AND
      i. Meets Milan criteria which meets **ONE** of the following:
         1. Single hepatocellular carcinoma, presence of tumor 5cm or less in diameter, **OR**
         2. Multiple tumors, each less than 3cm in diameter and no extrahepatic manifestations of the cancer or evidence of vascular invasion of the tumor.

AND ALL of the following:

1. Sovaldi and Ribavirin are **NOT** to be used as monotherapy
2. Patient is **NOT** taking concurrent therapy with Pegasys or Pegintron
3. Absence of renal impairment

   a. eGFR must be > 30mL/min/1.73m^2
4. Absence of end stage renal disease (ESRD)
5. Patient does **NOT** have decompensated cirrhosis
6. Patient has **NOT** had a liver transplant
7. Therapy will be discontinued if liver transplantation occurs
8. Absence of significant or unstable cardiac disease
9. Neither the patient nor the partner of the patient is pregnant
10. If patient or their partner are of child bearing age, the patient has been or will be instructed to practice effective contraception during therapy and for 6 months after stopping ribavirin therapy

Prior - Approval Limits

Duration

Genotype 1 without hepatocellular carcinoma(s):
24 weeks Sovaldi (168 tablets per 168 days) / 24 weeks Ribavirin

Genotype 2 without hepatocellular carcinoma(s):
12 weeks Sovaldi (84 tablets per 84 days) / 12 weeks Ribavirin

Genotype 3 without hepatocellular carcinoma(s):
24 weeks Sovaldi (168 tablets per 168 days) / 24 weeks Ribavirin

Genotype 1,2,3,or 4 with hepatocellular carcinoma(s):
24 weeks Sovaldi (168 tablets per 168 days) / 24 weeks Ribavirin

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Prior – Approval *Renewal* Requirements

Same as above

Prior - Approval *Renewal* Limits

Duration

Genotype 1, 2, 3 without hepatocellular carcinoma(s):
None

Genotype 1, 2, 3, 4 with hepatocellular carcinoma(s):
24 weeks Sovaldi (168 tablets per 168 days) / 24 weeks Ribavirin

Sovaldi
(sofosbuvir)

Sovaldi (sofosbuvir) with (PEGASYS or PEGINTRON) AND RIBAVIRIN

Sovaldi (sofosbuvir) with PEGASYS or PEGINTRON (peginterferon alfa-2b**,**
AND RIBAVIRIN
(Copegus, Rebetol, Ribapak, Ribasphere, Ribatabs, ribavirin - all strengths)

Pre - PA Allowance
None

Prior-Approval Requirements
Age 18 years of age or older

Diagnosis

Patient must have the following:

Chronic Hepatitis C

AND ALL of the following:

1. Viral genotype 1 or 4
2. Sovaldi and Ribavirin will **NOT** be used as monotherapy
3. Patient does **NOT** have hepatocellular carcinoma awaiting transplant (these patients should be treated with Sovaldi and ribavirin without interferon)
4. Absence of renal impairment
    a. eGFR must be > 30mL/min/1.73m^2
5. Absence of end stage renal disease (ESRD)
6. Patient does **NOT** have decompensated cirrhosis
7. Patient has **NOT** had a liver transplant
8. Absence of significant or unstable cardiac disease
9. Neither the patient nor the partner of the patient is pregnant
10. If patient or their partner are of child bearing age, the patient has been or will be instructed to practice effective contraception during therapy and for 6 months after stopping ribavirin therapy

Prior - Approval Limits
Duration

Sovaldi 12 weeks (84 tablets for 84 days)
Pegasys 12 weeks / Ribavirin 12 weeks

Sovaldi
(sofosbuvir)

Prior – Approval *Renewal* Requirements
None

Hepatitis Prior Authorization & Fax Order Form

Please indicate the intention of this request:

☐ Prior authorization and Cigna Home Delivery Pharmacy to fill ***Please deliver by:*** _____

☐ Prior authorization only (or call (800) 244-6224)

Order #:_____ **Referral Source Code:**_____ **Fax:** 1.800.351.3616 **Phone:** 1.800.351.3606

PATIENT INFORMATION (Please Print)		PHYSICIAN INFORMATION		
PATIENT NAME:	DATE OF BIRTH :	NAME:		
HEALTH CARE ID #:	GENDER: ☐ M ☐ F	DEA #:	NPI:	TIN:
HOME PHONE:	ALT PHONE:	ADDRESS: (Street/Suite #) (City) (State) (Zip Code)		
ADDRESS: (Street) (City) (State) (Zip Code)				
ALLERGIES: If no allergies are specified, for new customers this indicates no known allergies and for existing customers this indicates no change from information previously provided to Cigna.		TELEPHONE:	FAX:	

SHIP MEDICATIONS TO: ☐ Patient's Home (Please provide all available patient phone numbers as they are REQUIRED for scheduling delivery.) ☐ Physician's Office

PRESCRIPTION INFORMATION

PEGASYS® (Peginterferon Alfa-2a - S0145): ☐ **180 mcg/0.5 ml Prefilled Syringe** ☐ **180 mcg/0.5ml Proclick** ☐ Pharmacy asks patient for preference	**Directions:** DIRECTIONS: ☐ Inject 180 mcg SQ weekly ☐ Other (please specify):	**Refills:** QTY/REFILLS ☐ 1 month supply _____ refills ☐ 3 month supply _____ refills ☐ Other: _____QTY _____ refills
PEGASYS® (Peginterferon Alfa-2a - S0145): ☐ **180 mcg/1 ml Vial** **Note: Concentration of Syringe vs. Vial**		
PEG-INTRON® (Peginterferon Alfa-2b – S0146): ☐ 50 mcg/0.5 ml **Vial** ☐ 50 mcg/0.5 ml **Redipen** ☐ 80 mcg/0.5 ml **Vial** ☐ 80 mcg/0.5 ml **Redipen** ☐ 120 mcg/0.5 ml **Vial** ☐ 120 mcg/0.5 ml **Redipen** ☐ 150 mcg/0.5 ml **Vial** ☐ 150 mcg/0.5 ml **Redipen**	DIRECTIONS: ☐ Inject 0.4 ml SQ weekly ☐ Inject 0.5 ml SQ weekly ☐ Other (please specify):	
INFERGEN® (Interferon Alfacon-1 – J9212): ☐ **9 mcg/0.3 ml Vial** ☐ **15 mcg/0.5 ml Vial**	DIRECTIONS: ☐ Inject 9 mcg SQ 3 times per week ☐ Inject 15 mcg SQ 3 times per week ☐ Other (please specify):	
Intron® A (Interferon alfa-2b, recombinant – J9215): **18 million units multidose vial** **3 million units/dose multidose pen** **Other:**	DIRECTIONS: Inject 3 million units 3 times a week IM or SQ Other (please specify):	QTY/REFILLS ☐ 1 month supply _____ refills ☐ 3 month supply _____ refills ☐ Other: _____QTY _____ refills
☐ **Rebetol®** 200 mg capsules ☐ **Copegus®** 200 mg tablets	DIRECTIONS: _____ QAM AND _____ QPM	QTY/REFILLS ☐ 1 month supply _____ refills ☐ 3 month supply _____ refills ☐ Other: _____QTY _____ refills
INCIVEK (Telaprevir) ☐ 375 mg tablets	DIRECTIONS: ☐ Take 750mg (2 tablets) by mouth 3 times a day with food containing 20gm of fat	QTY/REFILLS ☐ 1 month supply _____ refills ☐ 3 month supply _____ refills ☐ Other: _____ QTY _____ refills
OLYSIO (Simeprevir) ☐ 150 mg tablets	DIRECTIONS: ☐ Take 1 capsule once daily with food	
SOVALDI (Sofosbuvir) ☐ 400 mg tablets	DIRECTIONS: ☐ Take 1 tablet once daily	
VICTRELIS (Boceprevir) ☐ 200 mg capsules	DIRECTIONS: ☐ Take 800mg (4 capsules) by mouth 3 times a day with food, start at day 29 (week 5).	

Hepatitis Prior Authorization & Fax Order Form

☐ **Lab reminder coordination and injection training**

SUPPLIES NEEDED *(if medication is to be administered in patient's home)*: If checked, please specify the size and type (if applicable):

☐ Syringes/Needles ☐ Swabs ☐ Sharps Container ☐ Other:

PHYSICIAN'S SIGNATURE: (Physician's signature indicates accuracy and completeness of prescription information)

In order for a brand name product to be dispensed, the prescriber must handwrite ***"Brand Necessary"*** or ***"Brand Medically Necessary"*** on the prescription

PATIENT NAME:	HEALTH CARE ID #:	DATE OF BIRTH:

The following levels are needed for approval of the below corresponding treatments.

HCV RNA Levels

Week of Therapy	Incivek	Olysio	Victrelis	Dual or Mono Therapy	Date Taken
Pretreatment			iu/ml*	iu/ml	
4	iu/ml	iu/ml	iu/ml*		
8			iu/ml*		
12	iu/ml	iu/ml	iu/ml	iu/ml	
24	iu/ml	iu/ml	iu/ml	iu/ml	
other	iu/ml	iu/ml	iu/ml	iu/ml	

*Pretreatment, 4 and 8 week levels are needed to determine length of Victrelis therapy

Clinical Information:

What is the patient's current weight? _____ ☐ lbs ☐ kg

Diagnosis related to use: ☐ (070.7) Hepatitis C ☐ Hepatitis B ☐ Other (please specify):

Does the patient have decompensated liver disease ☐ Yes ☐ No

(e.g. *of decompensated liver disease include: Ascites, Hepatic Encephalopathy, bleeding esophagogastric varicie*)?

What is the patient's genotype? ☐ 1 or 1a ☐ 1b ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ Other:

(if requesting **Olysio** and patient has genotype 1 or 1a) Has your patient been screened for one of the following: boceprevir resistance, telaprevir resistance, HCV drug resistance, NC3/4 resistance, or Q80K polymorphism?

☐ yes and resistance was detected

☐ yes and resistance was NOT detected

☐ no, this testing was not done

Does the patient have HIV/AIDS? ☐ Yes ☐ No

Does the patient have bridging fibrosis? ☐ Yes ☐ No

Does the patient have cirrhosis? ☐ Yes ☐ No

Has your patient had failure, contraindication, or intolerance to any of the following? (check all that apply)

☐ Infergen ☐ Intron ☐ Pegasys ☐ PegIntron ☐ Other_____

Has the patient previously taken Pegasys or Peg-Intron plus ribavirin? ☐ Yes ☐ No

If *yes*: Which one of the following describes previous therapy:

- ☐ completed therapy but relapsed
- ☐ partial response
- ☐ stopped treatment early (weeks completed _____)
- ☐ no response (did not have at least a 2 log drop in HCV after 12 weeks of prior treatment)

If *no*: Is the patient currently on therapy? ☐ Yes ☐ No

How many weeks has the patient completed? _____ weeks

Date started therapy? __/__/__

Does your patient have a contraindication to any of the following:

☐ Pegasys ☐ PegIntron ☐ Incivek ☐ Olysio ☐ Sovaldi ☐ Victrelis ☐ Other

Please explain:

Infergen requests:

Did the patient have intolerance to treatment with Pegasys or Peg-Intron? ☐ Yes ☐ No

Hepatitis Prior Authorization & Fax Order Form

For Incivek, Olysio, Sovaldi, or Victrelis requests:

Will this be used in combination with ribavirin? ☐ Yes ☐ No

Will this be used in combination with Pegasys or Peg-Intron? ☐ Yes ☐ No

For **Sovaldi** requests:

Does your patient also have a diagnosis of hepatocellular carcinoma (HCC, hepatocellular cancer, malignant hepatoma? ☐ Yes ☐ No

(if HCC) Has your patient previously had a liver transplant? ☐ Yes ☐ No

(if HCC) Is your patient waiting to undergo a liver transplant? ☐ Yes ☐ No

(if yes) Does your patient meet MILAN criteria for liver transplantation? ☐ Yes ☐ No

(Please note: there are different preferred products depending on your patient's plan. Please refer to the applicable Cigna health care professional resource [e.g. cignaforhcp.com] to determine benefit availability and the terms and conditions of coverage

Additional pertinent information:

PHYSICIAN'S SIGNATURE: (Physician's signature indicates accuracy and completeness of prescription information)

Our drug list can be viewed online at http://www.cigna.com. Prior authorization requests may also be submitted by calling (800) 244-6224. V010414

v1/1/14

Cigna Preferred Status:

- It is the decision of the prescribing physician in the exercise of his/her independent clinical judgment to determine which medication to prescribe. Coverage is not limited to the preferred drug.
- Cigna may receive payments from manufacturers whose medications are included on the Preferred Specialty (Injectable) Drug List. These payments may or may not be shared with the member's benefit plan dependent on the contractual arrangement between the plan and Cigna.
- Depending upon plan design, market conditions, the extent to which manufacturers' payments are shared with the member's benefit plan, and other factors as of the date of service, the preferred medication may or may not represent the lowest cost medication within the therapeutic class for the member and/or the benefit plan.
- Cigna reserves the right to make changes to its Preferred Specialty (Injectable) Drug List without notice.

HealthNet Coverage Policy

SOVALDI® (sofosbuvir)

NATL

Coverage of drugs is first determined by the member's pharmacy or medical benefit. Please consult with or refer to the Evidence of Coverage document.

1. FDA Approved Indications:
    - Indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. Sovaldi efficacy has been established in subjects with hepatitis C virus (HCV) genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplant) and those with HCV/HIV-1 co-infection.
2. Health Net Approved Indications and Usage Guidelines:
    - Diagnosis of CHC confirmed by detectable serum HCV RNA by quantitative assay. Genotype is required to determine length of approval.

      AND

    - Liver biopsy showing fibrosis corresponding to a Metavir score of greater than or equal to 2 or Ishak score of greater than or equal to 3 or other accepted test demonstrating liver fibrosis

      AND

    - Prescribed by or in consultation with a gastroenterologist, hepatologist or infectious disease physician.

      AND

    - For genotype 1 and 4 CHC: should be used as triple therapy in combination with peginterferon alfa and ribavirin or as double therapy in combination with ribavirin for patients who are interferon ineligible (patients in whom interferon therapy is contraindicated due to such conditions as anemia, alcohol abuse, advanced or decompensated cirrhosis, or severe psychiatric disorder) or interferon-intolerant (patients who discontinued interferon therapy prematurely due to side effects)

OR

- For genotype 2 or 3 CHC: must be used in combination with ribavirin

OR

- For treatment of CHC in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation): must be used in combination with ribavirin. Milan criteria is defined as 1 lesion ≤5 cm, up to 3 lesions each of which are ≤3 cm, and no extrahepatic manifestations/no vascular invasion.

3. Coverage is Not Authorized For:
    - Treatment of HCV as monotherapy.
    - Quadruple therapy (Sovaldi+(Olysio, Incivek,or VIctrelis)+peginterferon+ribavirin) combination
    - Treatment regimen that patient who has failed therapy with an NS3/4A protease inhibitor (e.g., boceprevir,simeprevir, telaprevir)
    - Non-FDA approved indications, which are not listed in the Health Net Approved Indications and Usage Guidelines section, unless there is sufficient documentation of efficacy and safety in the published literature
    - Post liver transplant
    - **Additional contraindications for use with peginterferon**
    - Autoimmune hepatitis
    - Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
    - Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before treatment
    - **Additional contraindications for use with ribavirin**
    - Women who are pregnant
    - Men whose female partners are pregnant
    - Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
    - Combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials
4. General Information:
    - Interim results from the COSMOS study evaluated Olysio and Sovaldi in HCV patients including treatment naive or previous null responder HCV patients. In HCV patients with advanced liver fibrosis or cirrhosis (METAVIR F3 or F4) 12 weeks all oral treatment with Olysio and Sovaldi with or without ribavirin led to SVR4 rates of 96% and

100%,respectively. These are interim results, further data are needed to prove efficacy.
- Gane et al. studied 10 patients treated with Sovaldi monotherapy for 12 weeks who had genotype 2 or 3 disease. The primary efficacy (SVR at 12 weeks after therapy stopped) was much lower (60%) on monotherapy versus 100% on combination therapy.
- The triple therapy (Sovaldi+peginterferon+ribavirin) combination study included patients with genotype 1, 4, 5 or 6 disease (NEUTRINO study).
- The POSITRON trial defines contraindications to interferon as those patients with psychiatric disorders (57% of patients in the trial) and autoimmune disorders (19% of patients in the trial). Unacceptable side effects with interferon were influenza-like symptoms (32% of patients), psychiatric disorders (20% of patients), thrombocytopenia (16% of patients) or local or systemic adverse reactions (12% of patients). Per AASLD Practice guideline (2009), additional characteristics of persons for whom therapy with interferon/ribavirin may be contraindicated include untreated thyroid disease, pregnancy, severe concurrent medical conditions (uncontrolled diabetes, uncontrolled hypertension, significant coronary heart disease) or solid organ transplant (renal, heart, lung).
- Preliminary results of a phase IIa trial evaluating combination therapy of Olysio and Sovaldi with or without ribavirin in genotype 1 patients was recently presented at the November 2013 AASLD meeting (COSMOS study [Combination of Simeprevir and sofosbuvir in HCV genotype 1 infected patients]). Preliminary results indicate SVR over 90% (approximately 187 patients).
- There are no data to support combination quadruple therapy with peginterferon, ribavirin, Sovaldi and a protease inhibitor (Olysio, Incivek or Victrelis).

5. Therapeutic Alternatives:

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
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6. *** Requires Prior Authorization**
7. Recommended Dosing Regimen and Authorization Limit:

Drug	Dosing Regimen	Authorization Limit
Sovaldi	Genotype 1 or 4: 400 mg PO QD	12 weeks in combination with peginterferon alfa + ribavirin

		OR 24 weeks in combination with ribavirin for interferon ineligible patients
Sovaldi	<u>Genotype 2:</u> 400 mg PO QD (in combination with ribavirin)	12 weeks
Sovaldi	<u>Genotype 3:</u> 400 mg PO QD (in combination with ribavirin)	24 weeks
Sovaldi	<u>Hepatocellular carcinoma patients awaiting liver transplantation:</u> 400 mg PO QD (in combination with ribavirin)	48 weeks or until liver transplantation, whichever occurs first

8. Product Availability:

   Sovaldi tablets: 400 mg

9. References:

   1. Sovaldi [Prescribing Information]. Foster City, CA: Gilead Sciences, Inc.; December 2013.

   2. Gane E, Stedman C, Hyland R et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013;36:34-44.

   3. Jacobson I, Gordon S, Kowdley K et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013;268:186-77.

   4. Lawitz E, Mangia A, Wyles D et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368:1878-1887.

   5. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334:693-9.

Draft Prepared: 09-DEC-13 SA
Approved By Health Net National P&T: 23-JAN-14, 13-FEB-14
Revised: 28-JAN-14 RJG, 12-FEB-14 RJG

Sovaldi™ (sofosbuvir)

Humana

Pharmacy Coverage Policy

Effective Date: December 19, 2013
Revision Date: January 9, 2014
Review Date: January 9, 2014
Line of Business: Commercial, Florida Medicaid, Medicare
Policy Type: Prior Authorization

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Disclaimer

Description

Sovaldi (sofosbuvir) is a nucleotide analog NS5B polymerase inhibitor.

Sovaldi (sofosbuvir) is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate which acts as a chain terminator when incorporated into HCV RNA by NS5B polymerase.

Sovaldi is indicated for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen.

Sofosbuvir is available as Sovaldi in 400 mg tablets.

Coverage Determination

Please note the following regarding medically accepted indications:

All reasonable efforts have been made to ensure consideration of medically accepted indications in this policy. Medically accepted indications are defined by CMS as those uses of a covered Part D drug that are approved under the federal Food, Drug and Cosmetic Act, or the use of which is supported by one or more citations included or approved for inclusion in any of the compendia described in section 1927(g)(1)(B)(i) of the Act. These compendia guide review of off-label and off-evidence prescribing and are subject to minimum evidence standards for each compendium. Currently, this review includes the following references when applicable and may be subject to change per CMS:

- American Hospital Formulary Service (AHFS) Compendium
- Thomson Micromedex/DrugDex (not Drug Points) Compendium
- National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium™
- Elsevier Gold Standard's Clinical Pharmacology Compendium

Sovaldi (sofosbuvir) will require prior authorization. This agent may be considered medically necessary when the following criteria are met:

Chronic Hepatitis C

- The member must have a diagnosis of chronic hepatitis C with compensated liver disease.
- The member must be at least 18 years of age.
- Baseline HCV RNA must be documented.
- Member has documented genotype 1, 2, 3, or 4 infection
  - Genotype 1
    - Member must have failed to achieve SVR on a prior regimen containing a HCV NS3/4A protease inhibitor
      - Sovaldi will be used in combination with peginterferon and ribavirin **OR**
      - Sovaldi will be used in combination with ribavirin for an interferon ineligible member defined as one of the following:
        - Contraindication to interferon therapy defined as: known hypersensitivity to interferon alfa, autoimmune hepatitis,

hepatic decompensation, pregnant females or male partners of pregnant females, hemoglobinopathies, creatinine clearance less than 50 mL/min, coadministration with didanosine

- Previous intolerance to an interferon alfa containing regimen resulting in discontinuation of therapy

- Genotype 2, 3
  - Sovaldi will be used in combination with ribavirin
- Genotype 4
  - Sovaldi will be used in combination with peginterferon and ribavirin

Chronic Hepatitis C with HIV co-infection

- The member must have a diagnosis of chronic hepatitis C with compensated liver disease.
- Member has HIV co-infection
- The member must be at least 18 years of age.
- Baseline HCV RNA must be documented.
- Member has documented genotype 1, 2, 3, or 4 infection
  - Genotype 1
    - Sovaldi will be used in combination with peginterferon and ribavirin OR
    - Sovaldi will be used in combination with ribavirin for an interferon ineligible member defined as one of the following:
      - Contraindication to interferon therapy defined as: known hypersensitivity to interferon alfa, autoimmune hepatitis, hepatic decompensation, pregnant females or male partners of pregnant females, hemoglobinopathies, creatinine clearance less than 50 mL/min, coadministration with didanosine
      - Previous intolerance to an interferon alfa containing regimen resulting in discontinuation of therapy
  - Genotype 2, 3
    - Sovaldi will be used in combination with ribavirin
  - Genotype 4
    - Sovaldi will be used in combination with peginterferon and ribavirin

Hepatocellular Carcinoma

- The member must have a diagnosis of chronic hepatitis C with compensated liver disease.
- The member must be at least 18 years of age.
- Member has documented genotype 1, 2, 3, or 4 infection
- Member has a diagnosis of hepatocellular carcinoma and is awaiting liver transplantation (meets Milan criteria)
- Sovaldi will be used in combination with ribavirin

Dosing

Chronic Hepatitis C and Chronic Hepatitis C with HIV co-infection:

- Genotype 1
  - Interferon-based dosing
    - Sovaldi 400 mg daily in combination with peginterferon alfa and ribavirin for 12 weeks
  - Interferon-ineligible
    - Sovaldi 400 mg daily in combination with ribavirin for 24 weeks
- Genotype 2
  - Sovaldi 400 mg daily in combination with ribavirin for 12 weeks
- Genotype 3
  - Sovaldi 400 mg daily in combination with ribavirin for 24 weeks
- Genotype 4
  - Sovaldi 400 mg daily in combination with peginterferon alfa and ribavirin for 12 weeks

Hepatocellular Carcinoma:

- Sovaldi 400 mg daily in combination with ribavirin for up to 48 weeks or until liver transplantation, whichever occurs first

Sovaldi (sofosbuvir) will be approved based on indication and treatment regimen or as determined through clinical review.

The quantity limit for all strengths of Sovaldi (sofosbuvir) is 28 tablets per 28 days.

Coverage Limitations

Sovaldi (sofosbuvir) therapy is not considered medically necessary for members with the following concomitant conditions:

- Monotherapy with Sovaldi
- Concurrent use with a HCV NS3/4A protease inhibitor.
- Coadministration with a potent P-glycoprotein (P-gp) inducer (e.g. rifampin, St. John's wort)
- Experimental/investigational use – Indications not supported by CMS recognized compendia or acceptable peer reviewed literature

Background

This is a prior authorization policy about Sovaldi (sofosbuvir).

- Ribavirin may cause birth defects and/or death of the exposed fetus and animal studies have shown that interferons have abortifacient effects. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
- Persistent viremia with HCV is virtually universal after liver transplantation, and the majority of patients develop recurrent liver injury.
- The Milan Criteria for liver transplantation:
  - No lesion larger than 5 cm
  - ≤ 3 lesions with diameter ≤ 3 cm
  - No extrahepatic involvement
  - No major vessel involvement

Provider Claims Codes

There are no provider claims codes associated with this policy.

Medical Terms

Sovaldi; sofosbuvir; chronic hepatitis C infection; HCV; HIV co-infection; hepatocellular carcinoma; pharmacy

References

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2013. URL: http://www.clinicalpharmacology.com. Updated November 2013.
2. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thompson Reuters (Healthcare) Inc. Updated periodically.

3. Ghany et al. AASLD Practice Guidelines: An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection. Hepatology 2011; 1433-1444.
4. Incivek [package insert]. Cambridge, MA: Vertex Pharmaceuticals, Inc; December 2012.
5. Murray KF, Carithers Jr. RL. AASLD Practice Guidelines: Evaluation of the Patient for Liver Transplantation. *Hepatology.* Vol. 41 (6).
6. Olysio [package insert]. Titusville, NJ: Janssen Therapeutics; 2013.
7. Pegasys [package insert]. South San Francisco, CA: Genetech USA; July 2013.
8. PegIntron [package insert]. Whitehouse Station, NJ: Schering Corporation, a subsidiary of Merck & Co., Inc; November 2013.
9. Sovaldi [package insert]. Foster City, CA: Gilead Sciences, Inc.; 2013.
10. Victrelis [package insert]. Whitehouse Station, NJ: Schering Corporation, a subsidiary of Merck & Co., Inc; February 2013.

References

AbbVie. (2014). AbbVie to present late-breaker Pearl-III study in patients with chronic hepatitis C at the 21st conference on retroviruses and opportunistic infections. March 3, 2014. Boston, MA: AbbVie. Retrieved March 6, 2014, from http://abbvie.mediaroom.com/2014-03-03-AbbVie-to-Present-Late-breaker-PEARL-III-Study-in-Patients-with-Chronic-Hepatitis-C-at-the-21st-Conference-on-Retroviruses-and-Opportunistic-Infections

American Association for the Study of Liver Diseases (AASLD). (2009). *Diagnosis, management and treatment of hepatitis C: An update*. Retrieved March 9, 2014, from http://www.aasld.org/practiceguidelines/documents/bookmarked%20practice%20guidelines/diagnosis_of_hep_c_update.aug%20_09pdf.pdf

American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). (2014). *Recommendations for testing, managing and treating hepatitis C.* Retrieved March 9, 2014, from http://www.hcvguidelines.org/sites/default/files/full_report.pdf

Bain, V.G., Bonacini, M., Govindarajan, S., Ma, M., Sherman, M., Gibas, A., et al. (2004). A multicentre study of the usefulness of liver biopsy in hepatitis C. *Journal of Viral Hepatitis, 11*(4), 375-82.

Blatt, L., Mutchnick, M., Tong, M., Klion, F., Lebovics, E., Freilich, B., et al. (2000). Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. *Journal of Viral Hepatitis, 7*(3), 196-202.

Centers for Disease Control (CDC). (2010). *Hepatitis C: General information*. Retrieved February 19, 2014, from http://www.cdc.gov/hepatitis/hcv/pdfs/hepcgeneralfactsheet.pdf

Centers for Disease Control (CDC). (2014). Hepatitis C FAQs for health professionals. Retrieved April 29, 2014, from http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section1

Chak, E., Talal, A., Sherman, K., Schiff, E., & Saab, S. (2011). Hepatitis C virus infection in USA: An estimate of true prevalence. *Liver International, 31*(8), 1090-1101.

Chen, J., Florian, J., Carter, W., Fleischer, R., Hammerstrom, T, Jadhav, P., et al. (2013). Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gasteroenterology, 144*(7), 1450-1455.

Chou, R., Hartung, D., Rahman, B., Wasson, N., Cottrell, E., & Fu, R. (2012). *Treatment for hepatitis C virus infection in adults. Comparative effectiveness review No. 76*. Prepared

by the Oregon Evidence-based Practice Center. Rockville, MD: Agency for Healthcare Research and Quality.

Davis, G.L., Alter, M.J., El-Serag, H., Poynard, T., & Jennings, L.W. (2010). Aging of hepatitis C virus (HCV)-infected persons in the United States: A multiple cohort model of HCV prevalence and disease progression. *Gastroenterology, 138*(2), 513-521.

Denniston, M., Jiles, R., Drobeniuc, J., Klevens, M., Ward, J., McQuillan, G., et al. (2014). Chronic hepatitis C virus infection in the United States: National Health and Nutrition Examination Survey 2003 to 2010. *Annals of Internal Medicine, 160*(5), 293-300.

European Association for the Study of the Liver (EASL). (2013). EASL clinical practice guidelines: Management of hepatitis C infection. *Journal of Hepatology, 60*(5), 392-420.

Food and Drug Administration (FDA). (2013a). *Guidance for industry: Chronic hepatitis C virus infection: Developing direct-acting antiviral drugs for treatment. Draft Guidance.* Baltimore, MD: US Department of Health and Human Services, Food and Drug Administration.

Food and Drug Administration (FDA). (2013b). *SOVALDI™ (sofosbuvir) tablets, for oral use*. Retrieved February 21, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf

Freeman, A.J., Dore, G.J., Law, M.G., Thorpe, M., Von Overbeck, J., Lloyd, A.R., et al. (2001). Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology*, *34*(4 Pt 1), 809-816.

Gane, E., Stedman, C., Hyland, R., Ding, X., Svarovskaia, E., & Symonds, W. (2013). Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *New England Journal of Medicine, 368*(1), 36-44.

Ghany, M., Strader, D., Thomas, D., & Seeff, B. (2009). AASLD practice guidelines: Diagnosis, management and treatment of hepatitis C: An update. *Hepatology, 49*(4), 1336-1374.

Ghany, M., Nelson, D., Strader, D., Thomas, D., & Seeff, L. (2011). An update on treatment of genotype 1 chronic hepatitis c virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology, 54*(4), 1433-1444.

Grebely, J., Prins, M., Helard, M., Cox, A., Osburn, W., Lauer, G., et al. (2012). Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: Towards a vaccine. *Lancet Infectious Diseases, 12* (5), 408-414.

Hartung, D., Zarin, D., Guise, J., McDonagh, M., Paynter, R., & Helfand, M. (2014). Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Annals of Internal Medicine, 160*(7), 477-484.

Hezode, C., Dorival, C., Zoulim, F., Poynard, T., Mathurin, P., Pol, S. et al. (2012). Safety of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin in cirrhotic non responders: First results of the French early access program. Presented at The International Liver Congress, Barcelona, Spain, April 18-22, 2012. Retrieved March 9, 2014, from http://mobile.ilcapp.eu/EASL_161/poster_23756/program.aspx

Imbert-Bismut, F., Ratziu, V., Pieroni, L., Charlotte, F., Benhamou, Y., Poynard, T., et al. (2001). Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: A prospective study. *Lancet, 357*(9262), 1069-75.

Jacobson, I., Gordon, S., Kowdley, K., Yoshida, E., Rodriguez-Torres, M., Sulkowski, M., et al. (2013a). Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *The New England Journal of Medicine, 368*(20), 1867-1877.

Jacobson, I.M., Ghalib, R.H., Rodriguez-Torres, M., Younossi, Z.M., Corregidor, A., Sulkowski, M.S., et al. (2013b). SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. [Abstract]. *Hepatology, 58*(6 Suppl), 1379A.

Kowdley, K., Lawitz, E., Crespo, I., Hassanein, T., Davis, M., & DeMicco, M. (2013). Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype 1 infection (ATOMIC): An open-label, randomized, multicenter phase II trial. *The Lancet, 381*(9883), 2100-2107.

Lawitz, E., Lalezari, J., Hassanein, T., Kowdley, K., Poordad, F., Sheikh, A., et al. (2013a). Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotype 1, 2 and 3 hepatitis c infection: A randomized, double-blind, phase 2 trial. *The Lancet, 13*(5), 401-408.

Lawitz, E., Mangia, A., Wyles, D., Rodriguez-Torres, M., Hassanein, T., Gordon, S., et al. (2013b). Sofosbuvir for previously untreated chronic hepatitis C infection. *The New England Journal of Medicine*, *368*(20), 1878-1887.

Lawitz, E., Ghalib, R., Rodriguez-Torres, M., Younossi, Z., Corregidor, A., Sulkowski, M., et. al. (2014, April). Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype 1 prior null-responders/treatment-naïve patients (COSMOS study): Primary endpoint (SVR12)

results in patients with Metavir F3-4 (Cohort 2). Paper presented at the conference of the European Association for the Study of the Liver. Retrieved April 24, 2014 from http://www.professionalabstracts.com/ilc2014/planner/index.php?go=abstract&action=abstract_show&absno=3655&

Levin, J. (2012). Prevalence, treatment, and comorbidities of hepatitis C infection (HCV) among patients with commercial and Medicaid insurance. *National AIDS Treatment Advocacy Project Digestive Disease Week*, May 18-21, 2013. Retrieved February 20, 2014, from http://www.natap.org/2013/DDW/DDW_03.htm

Louie, K., Laurent, S., Forssen, U., Mundy, L., & Pimenta, J. (2012). The high comorbidity burden of the hepatitis c virus infected population in the United States. *BMC Infectious Diseases, 12*(86), 1-11.

McCombs, J., Matsuda, T., Tonnu-Mihara, I., Saab, S., Hines, P., L'Italien, G., et al. (2014). The risk of long-term morbidity and mortality in patients with chronic hepatitis C: Results from an analysis of data from a Department of Veterans Affairs clinical registry. *Journal of the American Medical Association Internal Medicine, 174*(2), 204-212.

Mishra, P. (2013). *New drug application medical review: Sofosbuvir (GS-7977*). Washington, D.C.: US Food and Drug Administration. Retrieved March 5 from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204671Orig1s000MedR.pdf

Montori, V.M., Jaexchke, R., Schunermann, H.J., Bhandari, M, Brozek, J.L., Devereaux, P.J., et al. (2004). Users' guide to detecting misleading claims in clinical research reports. *British Medical Journal, 329*(6), 1093-1096.

Osinusi, A., Meissner, E., Lee, Y., Bon, D., Heytens, L., Nelson, A., et al. (2013). Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: A randomized clinical trial. *Journal of the American Medical Association, 310*(8), 804-811.

Parkes, J., Guha, I.N., Roderick, .P, & Rosenberg, W. (2006). Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *Journal of Hepatology, 44*(3), 462-74.

Prasad, V., Vandross, A., Toomey, C., Cheung, M., Rho, J., Quinn, S., et al. (2013). A decade of reversal: An analysis of 146 contraindicated medical practices. *Mayo Clinic Proceedings, 88*(8), 790-798.

Robison, J. (2013). Gilead Sciences $1,000 per day Solvaldi pills ready to launch. *The Motley Fool*, 13 December 2013. Retrieved February 21, 2014, from

http://www.fool.com/investing/general/2013/12/13/gilead-sciences-1000-per-day-sovaldi-pills-ready-t.aspx

Rodriguez-Torres, M., Lawitz, E., Kowdley, K., Nelson, D., DeJesus, E., et al. (2013). Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment naïve patients with HCV genotype 1: A randomized, 28-day, dose-ranging trial. *Journal of Hepatology, 58*(4), 663-668.

Scottish Intercollegiate Guidelines Network (SIGN). (2013). *Management of hepatitis C*. Edinburgh: (SIGN publication no. 133). Retrieved February 21, 2014 from http://www.sign.ac.uk/pdf/sign133.pdf

Sulkowski, M., Jacobson, I., Ghalib R., Rodriguez-Torres, M. Younossi, Z., Corredidor, A., et. al. (2014, April). *Once-daily simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype 1 prior null responders with Metavir F0-2: COSMOS study subgroup analysis.* Paper presented at the conference of the European Association for the Study of the Liver. Retrieved April 24, 2014 from http://www.professionalabstracts.com/ilc2014/planner/index.php?go=abstract&action=abstract_show&absno=2733&

Thein, H.H., Yi, Q., Dore, G.J., & Krahn, M.D. (2008). Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. *Hepatology,* 48(2), 418-431.

Thorlund, K., Druyts, E., & Mills, E. (2014). SVR 12 is higher than SVR24 in treatment-naïve hepatitis C genotype 1 patients treated with peginterferon plus ribavirin. *Clinical Epidemiology, 6*, 49-58.

Tice, J., Ollendorf, D., & Pearson, S. (2014). *The comparative clinical effectiveness and value of simeprevir and sofosbuvir in the treatment of chronic hepatitis C infection*. Draft report. Boston, MA: The Institute for Clinical & Economic Review. Retrieved February 12, 2014, from http://ctaf.org/sites/default/files/assessments/CTAF_Hep_C_Draft_021214.pdf

United States Department of Veterans Affairs. (2013). *Viral hepatitis*. Retrieved February 21, 2014, from http://www.hepatitis.va.gov/patient/faqs/treatment-success.asp

United States Preventive Services Task Force (USPSTF). (2013). *Screening for hepatitis C virus infection in adults*. Retrieved April 29, 2014, from http://www.uspreventiveservicestaskforce.org/uspstf12/hepc/hepcfact.pdf

Van der Meer, A., Veldt, B., Feld, J., Wedemeyer, H., Dufour, J., Lammert, F., et al. (2012). Association between sustained virological response and all-cause mortality among

patients with chronic hepatitis C and advanced hepatic fibrosis. *Journal of the American Medical Association, 308*(24), 2584-2593.

Veterans Health Administration (VHA) Pharmacy Benefits Management Services, the Medical Advisory Panel, VISN Pharmacist Executives, and the Office of Public Health. (2014). *Interim considerations for use: simeprevir in combination with peginterferon alfa and ribavirin, sofosbuvir in combination with peginterferon alfa and ribavirin, sofosbuvir in combination with ribavirin.* Retrieved March 8, 2014, from www.pbm.va.gov/clinicalguidance/clinicalrecommendations/interim_considerations_simeprevir_sofosbuvir_2.doc

Yee, H.S., Chang, M.F., Pocha, C., Lim, J., Ross, D., Morgan, T.R., et al. (2012.) Update on the management and treatment of hepatitis C virus infection: Recommendation from the Department of Veterans Affairs Hepatitis Resource Center Program and the National Hepatitis C Program Office. *American Journal of Gastroenterology, 107*(5), 669-89.

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD

IDSA

Infectious Diseases Society of America

Recommendations for Testing, Managing, and Treating Hepatitis C

Collaborating Partner

IAS–USA

International Antiviral Society–USA

TABLE OF CONTENTS

INTRODUCTION

The landscape of treatment for hepatitis C virus (HCV) infection has evolved substantially since the introduction of highly effective HCV protease inhibitor therapies in 2011. The pace of change is expected to increase rapidly, as numerous new drugs with different mechanisms of action will likely become available over the next few years. To provide healthcare professionals with timely guidance as new therapies are available and integrated into HCV regimens, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management. The International Antiviral Society–USA (IAS–USA) provides the structure and assistance to sustain the process that represents the work of leading authorities in hepatitis C prevention, diagnosis, and treatment.

The AASLD/IDSA hepatitis C Guidance addresses management issues ranging from testing and linkage to care, the crucial first steps toward improving health outcomes for HCV-infected persons, to the optimal treatment regimen in particular patient situations. Recommendations are based on evidence and are rapidly updated as new data from peer-reviewed evidence become available. For each treatment option, recommendations reflect the best possible management for a given patient and a given point of disease progression. Recommendations are graded with regard to the level of the evidence and strength of the recommendation. The AASLD/IDSA hepatitis C Guidance is supported by the membership-based societies and not by pharmaceutical companies or other commercial interests. The Boards of Directors of AASLD and IDSA have appointed an oversight panel of 5 co-chairs and have selected panel members from the 2 societies based on their expertise in hepatitis C research and care. Likewise, the Guidance development process is generally consistent with that used by the IAS–USA (https://www.iasusa.org/about/program-development-policy).

This Guidance should be considered a "living document" in that new sections will be added (eg, Who and When to Initiate Treatment, and Monitoring Patients Who are On or Have Completed Therapy are coming soon) and the Guidance will be updated frequently as new information and treatments become available. This continually evolving report provides guidance on FDA-approved regimens. At times, it may also recommend off-label use of certain drugs or tests or provide guidance for regimens not yet approved by FDA. Readers should consult prescribing information and other resources for further information. Of note, the choice of treatment may, in the future, be further guided by data from cost-effectiveness studies.

METHODS

The Guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases, using an evidence-based review of information that is largely available to healthcare practitioners. The process and detailed methods for developing the Guidance are detailed in Methods Table 1. Recommendations were graded according to the strength of the recommendation and quality of the supporting evidence (see Methods Table 2). Commonly used abbreviations are expanded in Methods Table 3.

Methods Table 1. Summary of the Process and Methods for the Guidance Development

Topic	Description
Statement of Need	The introduction of direct-acting agents against HCV in 2011 has rapidly changed the treatment of HCV and the timely diagnosis of infection remains essential. This ever increasing pace of change anticipates numerous additional therapies in the next few years, requiring timely guidance on how each new development changes practice for health care professionals.
Goal of the Guidance	The goal of the Guidance is to provide up-to-date recommendations to health care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the United States, considering the best available evidence. The Guidance will be updated regularly, as new data, information, and tools and treatments become available. The initial recommendations address 4 areas of priority: screening, testing, and linkage to care; initial treatment regimens in persons for whom the decision to treat has been made; retreatment regimens and considerations for persons for whom the decision to treat has been made; and treatment in unique patient populations.
Panel members	The Panel members were chosen because of their expertise in the diagnosis, management, and treatment of HCV infection in terms of research and patient care. Members from the fields of hepatology and infectious diseases are included. Members were appointed by the respective Sponsor Societies after vetting by an appointed Sponsor Society committee. At least 1 representative from the hepatitis C community serves on the Panel. The Panel chairs were appointed by the Society boards, 2 each from the Sponsor Societies and 1 representing the Collaborating Partner. All Panel chairs and members serve as volunteers (not compensated) for defined terms (3 years), which may be renewed.
Conflict of interest management	Financial conflict of interest statements, with regard to personal (ie, direct payment to the individual) and institutional financial relationships with commercial entities that have products in the field of hepatitis C, for the prior year of all chairs and members under consideration were reviewed by the Sponsor Societies and Collaborating Partner during the vetting processes. Panel members under consideration were given the opportunity to divest or begin divesting themselves of any nonconforming personal conflicts of interest before being confirmed to the Panel. The Panel is composed of members with personal financial relationships with commercial entities and those with no such personal financial relationships with commercial entities at the time that each Panel member was confirmed. Designation of financial interest was determined based on each Sponsor Society's criteria (eg, limits on annual compensation from any particular commercial entity, absence of employment with a commercial entity, absence of equity or options in the relevant commercial entity, absence of service on company speakers' bureaus and company paid lectureships). More details on the management of conflicts of interest can be found on the organizations' websites. At the first in-person meeting of the full Panel, each chair and member read his or her disclosure statement to the group; members are given the opportunity to recuse themselves (or be recused) from particular topic areas where there is a perceived conflict of interest that cannot be resolved. Panel member direct personal and institutional/general research financial disclosure information was provided at the beginning of this project (October 2013). Financial disclosures for each individual Panel member can be accessed from the Panel members' pages.
Intended Audience	Medical practitioners especially those who provide care to or manage patients with hepatitis C.
Sponsors, funding, and collaborating partner	The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) are the Sponsors of the Guidance and provide financial support. The International Antiviral Society–USA (IAS–USA) is the Collaborating Partner responsible for providing expertise and managing the Panel and the Guidance development process. Centers for Disease Control and Prevention (CDC) provided financial support for the gathering and review of evidence related to hepatitis C screening and testing recommendations and interventions to implement HCV screening in clinical settings.

Evidence identification and collection	The Guidance was developed using an evidence-based review of information that is largely available to health care practitioners. Data from the following sources are considered by Panel members when making recommendations: research published in the peer-reviewed literature or presented at major national or international scientific conferences, safety warnings from FDA or other regulatory agencies or from manufacturers, drug interaction data, prescribing information from FDA-approved products, and registration data for new products under FDA review. Unpublished or presented reports, data on file, and personal communications are generally not considered. Panel members were appointed based on their collective broad knowledge of available data and current research in the field. These experts were responsible for initially identifying and discussing relevant data, including recent reports from scientific conferences. An initial literature search was conducted on November 4, 2013, to ensure that the Panel addressed all relevant published data. A total of 3939 unique citations were retrieved. Medical subject headings and free text terms were combined to maximize retrieval of relevant citations from the PubMed, Scopus, EMBASE, and Web of Science databases. To be considered for inclusion, articles were required to have been published in English from 2010 to the present. Review articles, studies using mice or rats, and in vitro studies were excluded from consideration. The Panel members regularly monitor the field for new evidence, and the literature search is updated as needed.
Grading of the evidence and RECOMMENDATIONS	The Guidance is presented in the form of RECOMMENDATIONS. Each RECOMMENDATION is graded in terms of the level of the evidence and strength of the recommendation, using a scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. (American Heart Association, 2014); (Shiffman, 2003) A summary of the supporting (and conflicting) evidence follows each RECOMMENDATION or set of RECOMMENDATIONS.
Data review and synthesis and preparation of RECOMMENDATIONS and supporting information	The Guidance was initially divided into 3 subsections: 1) Testing and Linkage to Care; 2) Choice of Regimen in Treatment-Naive Patients For Whom the Decision to Treat Has Been Made, and 3) Retreatment for Patients in Whom the decision to treat has been made. It was later decided to make treatment for unique patient populations a separate section. Subgroups of the panel were assigned to collect, review, and prepare initial draft RECOMMENDATIONS. Draft RECOMMENDATIONS were reviewed at the first full Panel meeting in October 2013. Subgroups of the Panel then met regularly by conference call and presented their updated RECOMMENDATIONS and supporting evidence at each of 3 full-Panel conference calls. Final approval of all RECOMMENDATIONS was made by full-Panel, general consensus. Initial recommendations and their grades were individually subject to Panel survey; panelists were given the opportunity to agree, disagree, and provide comment. This procedure helped identify any disagreement or inconsistency between Panel members for each recommendation. Sponsor Societies have final review and approval of each recommendation prior to release of the Guidance on the website, www.hcvguidelines.org.
Update Process	The Guidance will be expanded to cover more management issues as needed, and will be updated on an ongoing basis. Panel members will regularly monitor the field for data that may warrant modification of the Guidance. Updates may be prompted by new publications or presentations at major national or international scientific conferences, new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety warnings, or other information that may have a substantial impact on the clinical care of patients. Updated RECOMMENDATIONS and ratings, once agreed on by the full Panel and approved by the Sponsor Societies, are posted on the Guidance website.
Abbreviations	Commonly used abbreviations in the text with their expansions are listed in Methods Table 3.
Opportunity for Comments	Evidence-based comments may be submitted to the Panel by email hcvguidelines@iasusa.org, or clicking on the “Send a comment to the Panel” button onwww.hcvguidelines.org/contact-us. The Panel considers evidence-based comments about the RECOMMENDATIONS, grades, and evidence summary, but should not be contacted for individual patient management questions.

Methods Table 2. Grading System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (**I**, **II**, or **III**) that represents the level of the evidence that supports the recommendation, and a letter (**A**, **B**, or **C**) that represents the strength of the recommendation.

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	**Description**
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Consensus opinion of experts, case studies, or standard of care

Adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. (American Heart Association, 2011); (Shiffman, 2003)

Methods Table 3. Commonly Used Abbreviations and Their Expansions

Abbreviation	Expansion or Notes
HCV	hepatitis C virus. In this Guidance "hepatitis C virus" and HCV refer to the virus. Hepatitis C and HCV infection or HCV disease refer to the resulting disease.
BOC	boceprevir
CrCl	creatinine clearance
CTP	Child Turcotte Pugh
DAA	direct-acting agent
ESRD	end-stage renal disease
IFN	interferon alfa
MELD	model for end-stage liver disease
MSM	men who have sex with men
OATP	organic anion-transporting polypeptide
P-gp	p-glycoprotein
PEG	peginterferon alfa
RAV	resistance-associated variants
RBV	ribavirin
RGT	response-guided therapy
RVR	rapid virologic response
sAg	surface antigen
SMV	simeprevir; used for the treatment of those with genotype 1 of hepatitis C virus (HCV) who have compensated liver disease, including cirrhosis
SOF	sofosbuvir; a nucleoside analog used in combination with other drugs for the treatment of hepatitis C virus (HCV) infection
SVR12 (or 24 or 48, etc)	sustained virologic response at 12 weeks (or at 24 weeks, or at 48 weeks, etc)
TVR	telaprevir; a direct-acting agent (DAA) to treat hepatitis C

Definition of Terms

Child Turcotte Pugh (CTP) classification of the severity of cirrhosis

	Class A	Class B	Class C
Total points	5–6	7–9	10–15
Factor	**1 Point**	**2 Points**	**3 Points**
Total bilirubin (µmol/L)	<34	34–50	>50
Serum albumin (g/L)	>35	28–35	<28
Prothrombin time/international normalized ratio	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

IFN-ineligible

IFN ineligible is defined as one or more of the below:

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- History of depression, or clinical features consistent with depression
- A baseline neutrophil count below 1500/µL, a baseline platelet count below 90,000/µL or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

Relapser

a person who has achieved an undetectable level of virus during a prior treatment course of PEG/RBV and relapsed after treatment was stopped

HCV TESTING AND LINKAGE TO CARE

A summary of recommendations for Testing and Linkage to Care is found in the box.

HCV testing is recommended at least once for persons born between 1945 and 1965.

Rating: Class I, Level B

Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

1. *Risk behaviors*
   - Injection-drug use (current or ever, including those who injected once)
   - Intranasal illicit drug use
2. *Risk exposures*
   - Long-term hemodialysis (ever)
   - Getting a tattoo in an unregulated setting
   - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood
   - Children born to HCV-infected women
   - Prior recipients of transfusions or organ transplants, including persons who:
     - were notified that they received blood from a donor who later tested positive for HCV infection
     - received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
     - received clotting factor concentrates produced before 1987
     - were ever incarcerated
3. *Other medical conditions*
   - HIV infection
   - Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels

Rating: Class I, Level B

Of the estimated 2.7 million to 3.9 million persons (1999 to 2008 National Health and Nutrition Examination Survey data [Armstrong, 2006]) chronically infected with HCV in the United States, 45% to 85% are unaware that they are infected. (Smith, 2012) Identification of those with active infection is the first step toward improving health outcomes among persons with HCV infection and preventing transmission. (Smith, 2012); (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998)

HCV testing is recommended in select populations based on demography, prior exposures, high-risk behaviors, and medical conditions. Recommendations for testing are based on HCV prevalence in these populations, proven benefits of care and treatment in reducing the risk of hepatocellular carcinoma and all-cause mortality, and the potential public health benefit of reducing transmission through early treatment, viral clearance, and reduced risk behaviors. (Smith, 2012); (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998)

HCV is primarily transmitted through percutaneous exposure to blood. Other modes of transmission include mother-to-infant and contaminated devices shared for non-injection drug use; sexual transmission also occurs but generally seems to be inefficient except among HIV-infected men who have unprotected sex with men. (Schmidt, 2014) The most important risk for HCV infection is injection-drug use, accounting for at least 60% of acute HCV infections in the United States. Health-care exposures are important sources of transmission, including the receipt of blood products before 1992 (after which routine screening of blood supply was implemented), receipt of clotting factor concentrates before 1987, long-term hemodialysis, needle-stick injuries among healthcare workers, and patient-to-patient transmission resulting from poor infection control practices. Other risk factors include having been born to an HCV-infected mother, having been incarcerated, and having received a tattoo in an unregulated setting. The importance of these risk factors might differ based on geographic location and population. (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998). An estimated 29% of incarcerated persons in North America are anti-HCV positive, supporting the

recommendation to test this population for HCV. (Larney, 2013) Because of shared transmission modes, persons with HIV infection are at risk for HCV; sexual transmission is a particular risk for HIV-infected men who have unprotected sex with men. (Hosein, 2013); (van de Laar, 2010) Recent data also support testing in all cadaveric and living solid-organ donors because of the risk of HCV infection posed to the recipient. (Seem, 2013); (Lai, 2013)

In 2012, CDC expanded its guidelines originally issued in 1998 (Centers for Disease Control and Prevention, 1998) for risk-based HCV testing with a recommendation to offer a 1-time HCV test to all persons born between 1945 and 1965 without prior ascertainment of HCV risk-factors. This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of HCV infections in part due to patient underreporting of their risk and provider limitations in ascertaining risk-factor information. Furthermore, persons in the 1945 to 1965 birth cohort accounted for nearly three-fourths of all HCV infections, with a 5-times higher prevalence (3.25%) than other persons, reflecting a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000 versus 15,000 in 2009). A recent retrospective review showed that 68% of persons with HCV infection would have been identified through a birth-cohort testing strategy, whereas only 27% would have been screened with the risk-based approach. (Mahajan, 2013) The cost-effectiveness of 1-time birth cohort testing is comparable to that of current risk-based screening strategies. (Smith, 2012)

CDC and the US Preventive Services Task Force (USPSTF) both recommend a 1-time HCV test in asymptomatic persons belonging to the 1945 to 1965 birth cohort and other persons based on exposures, behaviors, and conditions that increase risk for HCV infection.

Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.

Rating: Class IIA, Level C

Evidence regarding the frequency of testing in persons at risk for ongoing exposure to HCV is lacking; therefore, clinicians should determine the periodicity of testing based on the risk of reinfection. Because of the high incidence of HCV infection among persons who inject drugs and among HIV-infected MSM who have unprotected sex (Aberg, 2013); (Linas, 2012); (Wandeler, 2012); (Witt, 2013); (Bravo, 2012); (Williams, 2011), at least annual HCV testing is recommended in these subgroups.

An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive RNA test.

Rating: Class I, Level A

Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered in persons who are immunocompromised.

Rating: Class I, Level C

Among persons suspected of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive.

Rating: Class I, Level C

Quantitative HCV RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).

Rating: Class I, Level A

Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.

Rating: Class I, Level A

If found to have positive results for anti-HCV test and negative results for HCV RNA by PCR, persons should be informed that they do not have evidence of current (active) HCV infection.

Rating: Class I, Level A

All persons recommended for HCV testing should first be tested for HCV antibody (anti-HCV) (Centers for Disease Control and Prevention [CDC], 2013); (Alter, 2003) using an FDA-approved test. FDA-approved tests include laboratory-based assays and a point-of-care assay (ie, OraQuick HCV Rapid Antibody Test [OraSure Technologies]). (Lee, 2011) The latter is an indirect immunoassay with a sensitivity and specificity similar to those of FDA-approved laboratory-based HCV antibody assays.

A positive test result for anti-HCV indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive test result. (Pawlotsky, 2002) Therefore, an HCV nucleic acid test (NAT) to detect viremia is necessary to confirm current (active) HCV infection and guide clinical management, including initiation of HCV treatment. HCV RNA testing should also be performed in persons with a negative anti-HCV test who are either immunocompromised (eg, persons receiving chronic hemodialysis) (KDIGO, 2008) or who might have been exposed to HCV within the last 6 months (including those who are possibly reinfected after previous spontaneous or treatment-related viral clearance) because these persons may be anti-HCV negative. An FDA-approved quantitative or qualitative NAT with a detection level of 25 IU/mL or lower should be used to detect HCV RNA. Testing and Linkage to Care Table 1 lists FDA-approved, commercially available anti-HCV screening assays. Testing and Linkage to Care Figure 1 shows the CDC-recommended testing algorithm.

Prior to the initiation of HCV therapy, quantitative HCV RNA testing is necessary to document the baseline level of viremia (ie, viral load), because the degree of initial viral decline is a crucial marker of the effectiveness of treatment. Testing for HCV genotype helps to guide selection of the most appropriate treatment regimen. Persons who have positive results for an anti-HCV test and negative results for HCV RNA by PCR should be informed that they do not have laboratory evidence of current (active) HCV infection. Additional HCV testing is typically unnecessary. However, some practitioners or persons may seek additional testing to learn if the HCV antibody test represents a remote HCV infection that has resolved or a false-positive result. For patients with no apparent risk for HCV infection, the likelihood of a false-positive HCV antibody test is directly related to the HCV prevalence in the tested population; false-positive test results for anti-HCV are most common for populations with a low prevalence of HCV infection. (Alter, 2003) If further testing is desired to distinguish between true positivity and biologic false positivity for HCV antibody, testing may be done with a second FDA-approved HCV antibody assay that is different from the assay used for initial antibody testing. A biologic false result should not occur with 2 different tests. (Vermeersch, 2008); (Centers for Disease Control and Prevention [CDC]), 2013) The HCV RNA test can be repeated when there is a high index of suspicion of infection or in patients with prior or ongoing risk factors for HCV infection.

Persons with current (active) HCV infection should receive education and interventions aimed at reducing progression of liver disease and preventing transmission of HCV.

Rating: Class IIa, Level B

1. *Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.*

   Rating: Class IIa, level B

2. *Evaluation for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection.*

   Rating: Class IIb, level B

3. *Evaluation for advanced fibrosis, using liver biopsy, imaging, or non-invasive markers, is recommended in all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and determine the need for initiating additional screening measures (eg, hepatocellular carcinoma [HCC] screening).*

   Rating: Class I, Level B

4. *Vaccination against hepatitis A and hepatitis B is recommended for all persons with HCV infection who are susceptible to these types of viral hepatitis.*

   Rating: Class IIa, Level C

5. *All persons with HCV infection should be provided education on how to avoid HCV transmission to others.*

   Rating: Class I, level C

In addition to receiving therapy, HCV-infected persons should be educated about how to prevent further damage to their liver. Most important is prevention of the potential deleterious effect of alcohol. Numerous studies have found a strong association between the use of excess alcohol and the development or progression of liver fibrosis and even the development of HCC. (Poynard, 1997); (Harris, 2001); (Wiley, 1998); (Corrao, 1998); (Bellentani, 1999); (Noda, 1996); (Safdar, 2004)

Excess alcohol intake may also cause steatohepatitis. The daily consumption of more than 50 grams of alcohol has a high likelihood of worsening fibrosis. Some studies indicate that daily consumption of smaller amounts of alcohol also have a deleterious effect on the liver; however, these data are controversial. (Westin, 2002) Alcohol screening and brief interventions such as those outlined by the National Institute of Alcohol Abuse and Alcoholism (http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm) have been demonstrated to reduce alcohol consumption and episodes of binge drinking in the general population and among HCV-infected persons who consume alcohol heavily.(Whitlock, 2004); (Dieperink, 2010); (Proeschold-Bell, 2012) Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist.

HBV and HIV coinfection have been associated with poorer prognosis of HCV in cohort studies. (Thein, 2008); (Zarski, 1998) Due to overlapping risk factors for these infections and additional benefits of their identification and treatment, persons with HCV should be tested for HIV antibody and HBsAg using standard assays for screening (Moyer, 2013); (Centers for Disease Control and Prevention, 2008) (http://www.aafp.org/afp/2008/0315/p819.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm) and counseled how to reduce their risk of acquiring these infections, including through HBV vaccination (see below).

Patients with obesity and metabolic syndrome having underlying insulin resistance are more prone to have nonalcoholic fatty liver disease, which is a risk factor for fibrosis progression in HCV-infected persons. (Hourigan, 1999); (Ortiz, 2002) Therefore, HCV-infected persons who are overweight or obese (defined by a body mass index 25 kg/m^2 or higher or 30 kg/m^2 or higher, respectively) should be counseled regarding strategies to reduce weight and improve insulin resistance via diet, exercise, and medical therapies. (Musso, 2010); (Shaw, 2006) Patients with HCV infection and hyperlipidemia or cardiovascular comorbidities may also benefit from various hypolipidemic drugs. Prospective studies have demonstrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease. (Lewis, 2007) Therefore, these agents should not be withheld in HCV-infected patients.

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Although patients with more advanced disease generally have a lower response to HCV therapy, they are also most likely to derive the greatest survival benefit. (Ghany, 2011) A liver biopsy can provide objective, semi-quantitative information regarding the amount and pattern of collagen or scar tissue in the liver, which can assist with treatment and monitoring plans. The Metavir fibrosis score (0-4) and Ishak fibrosis score (0-6) are commonly used to score the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation, or of hepatic steatosis, and help exclude competing causes of liver injury. (Kleiner, 2005) However, the procedure has a low but real risk of complications, and sampling artifact makes its serial use in most patients less desirable. (Regev, 2002) Non-invasive methods frequently used to estimate liver disease severity include a liver-directed physical exam (normal in most patients), routine blood tests (eg, serum alanine transaminase, albumin, bilirubin, international normalized ratio levels, and complete cell blood counts with platelets), serum fibrosis marker panels, liver imaging (eg, ultrasound, computed tomography scan), and liver elastography. Simple blood tests (eg, serum aspartate aminotransferase/platelet ratio index) (Wai, 2003) (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri) and assessment of liver surface nodularity and spleen size by liver ultrasound or other cross-sectional imaging modalities can help determine if patients with HCV have occult portal hypertension, which is associated with a greater likelihood of developing future hepatic complications in untreated patients. (Chou, 2013); (Rockey, 2006) Liver elastography can provide instant information regarding liver stiffness at the point-of-care but can only reliably distinguish cirrhosis from non-cirrhosis. (Castera, 2012) Since persons with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease, they require more frequent follow up; these persons also should avoid ulcerogenic drugs and receive ongoing imaging surveillance for liver cancer and varices. (Sangiovanni, 2006); (Fontana, 2010)

Exposure to infected blood is the primary mode of HCV transmission. HCV-infected persons must be informed of the precautions needed to avoid exposing others to infected blood. This is particularly important for persons who use injection drugs, given that HCV transmission in this population primarily results from the sharing of needles and other infected implements. Recently, epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described. (van de Laar, 2009); (Urbanus, 2009); (Fierer, 2008) Testing and Linkage Table 2 outlines measures to avoid HCV transmission. HCV is not spread by sneezing, hugging, holding hands, coughing, or sharing eating utensils or drinking glasses, nor is it transmitted through food or water.

Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.

Rating: Class IIa, level C

The definition of evaluation is: *Patient has attended a medical care visit with a practitioner able to complete a full assessment, the pros and cons of antiviral therapy have been discussed, and the patient has been transitioned into treatment, if appropriate.*

Improvement in identification of current (active) HCV infection and advances in treatment regimens will have limited impact on HCV-related morbidity and mortality without concomitant improvement in linkage to care. All patients with current HCV infection and a positive HCV RNA test result should be evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care is required for persons with HCV infection who have advanced fibrosis/cirrhosis (stage III or above on METAVIR scale), including possible referral for consideration of liver transplantation. In the United States, only an estimated 13% to 18% of persons chronically infected with HCV receive treatment. (Holmberg, 2013) Lack of appropriate practitioner assessment and delays in linkage to care can result in negative health outcomes. Further, patients who are lost to follow-up fail to benefit from evolving evaluation and treatment options.

Commonly cited patient-related barriers to treatment initiation include contraindications to treatment (eg, medical or psychiatric comorbidities), lack of acceptance of treatment (eg, asymptomatic nature of disease, competing priorities, low treatment efficacy, and long treatment duration and adverse effects), and lack of access to treatment (eg, cost and distance to specialist). (Khokhar, 2007); (Arora, 2011); (Clark, 2012) Common practitioner–related barriers include perceived patient-related barriers (eg, fear of adverse effects, treatment duration, cost, and effectiveness), lack of expertise in HCV treatment, lack of specialty referral resources, resistance to treating persons currently using illicit drugs or alcohol, and concern about cost of HCV treatment. (Morrill, 2005); (Reilley, 2013); (McGowan, 2013) Some possible strategies to address these barriers are listed in Testing and Linkage to Care Table 3. One strategy that addresses several barriers is co-localization of HCV screening, evaluation, and treatment with other medical or social services. Co-localization has already been applied to settings with a high prevalence of HCV infection (eg, correctional facilities and programs providing needle exchange, substance abuse treatment, and methadone maintenance) but is not uniformly available. (Islam, 2012); (Stein, 2012); (Bruggmann, 2013)

A strategy that addresses lack of access to specialists (a primary barrier to hepatitis C care) is participation in models involving close collaboration between primary-care practitioners and subspecialists. (Arora, 2011); (Rossaro, 2013); (Miller, 2012) Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists. (Arora, 2011); (Rossaro, 2013) For example, Project ECHO (Extension for Community Healthcare Outcomes [http://www.echohcvexperts.com]) uses videoconferencing to enhance primary care practitioner capacity in rendering HCV care and treatment to New Mexico's large rural and underserved population. (Rossaro, 2013) Through case-based learning and real-time feedback from a multidisciplinary team of specialists (ie, gastroenterology, infectious diseases, pharmacology, and psychiatry practitioners), Project ECHO has expanded access to HCV infection treatment in populations that might have otherwise remained untreated.

Additional strategies of enhancing linkage to care could be adapted from other fields, such as tuberculosis and HIV, but remain to be evaluated for HCV infection. For example, use of directly observed therapy has enhanced adherence to TB treatment, and use of case managers and patient navigators has reduced loss of follow-up in HIV care. (Govindasamy, 2012) An assessment of efficacy and comparative effectiveness of these strategies is a crucial area of future research for patients with HCV infection. Replication and expansion of best practices and new models for linkage to HCV care will also be crucial to maximize the public health impact of newer treatment paradigms.

Testing and Linkage To Care Box. Summary of Recommendations for Testing and Linkage to Care

HCV testing is recommended at least once for persons born between 1945 and 1965.

Rating: Class I, Level B

Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

1. *Risk behaviors*
   - Injection drug use (current or ever, including those who injected once)
   - Intranasal illicit drug use
2. *Risk exposures*
   - Long-term hemodialysis (ever)
   - Getting a tattoo in an unregulated setting
   - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood
   - Children born to HCV-infected women
   - Prior recipients of transfusions or organ transplants, including persons who:
     - were notified that they received blood from a donor who later tested positive for HCV infection
     - received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
     - received clotting factor concentrates produced before 1987
     - were ever Incarcerated
3. *Other medical conditions*
   - HIV infection
   - Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels

Rating: Class I, Level B

Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.

Rating: Class IIA, Level C

An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive RNA test.

Rating: Class I, Level A

Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered in persons who are immunocompromised.

Rating: Class I, Level C

Among persons suspected of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive.

Rating: Class I, Level C

Quantitative HCV RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).

Rating: Class I, Level A

Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.

Rating: Class I, Level A

If found to have positive results for anti-HCV test and negative results for HCV RNA by PCR, persons should be informed that they do not have evidence of current (active) HCV infection.

Rating: Class I, Level A

Persons with current (active) HCV infection should receive education and interventions aimed at reducing progression of liver disease and preventing transmission of HCV.

Rating: Class IIa, Level B

1. *Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.*

   Rating: Class IIa, level B

2. *Evaluation for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection.*

   Rating: Class IIb, level B

3. *Evaluation for advanced fibrosis is recommended using liver biopsy, imaging, or non-invasive markers in all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional screening measures (eg, hepatocellular carcinoma [HCC] screening).*

   Rating: Class I, Level B

4. *Vaccination against hepatitis A and hepatitis B is recommended for all persons with HCV infection who are susceptible to these types of viral hepatitis.*

   Rating: Class IIa, Level C

5. *All persons with HCV infection should be provided education on how to avoid HCV transmission to others.*

   Rating: Class I, level C

Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.

Rating: Class IIa, level C

Testing and Linkage to Care Table 1. FDA-approved, Commercially Available Anti-HCV Screening Assays

Assay	Manufacturer	Format
Abbott HCV EIA 2.0	Abbott	EIA (Manual)
Advia Centaur HCV	Siemens	CIA (Automated)
ARCHITECT Anti-HCV	Abbott	CMIA (Automated)
AxSYM Anti-HCV	Abbott	MEIA (Automated)
OraQuick HCV Rapid Antibody Test	OraSure	Immunochromatographic (Manual)
Ortho HCV Version 3.0 EIA	Ortho	EIA (Manual)
VITROS Anti-HCV	Ortho	CIA (Automated)

Anti-HCV = HCV antibody; EIA = enzyme immunoassay; CIA = chemiluminescent immunoassay; MEIA = microparticle enzyme immunoassay; CMIA = chemiluminescent microparticle immunoassay

Table prepared by Saleem Kamili, PhD, Centers for Disease Control and Prevention.

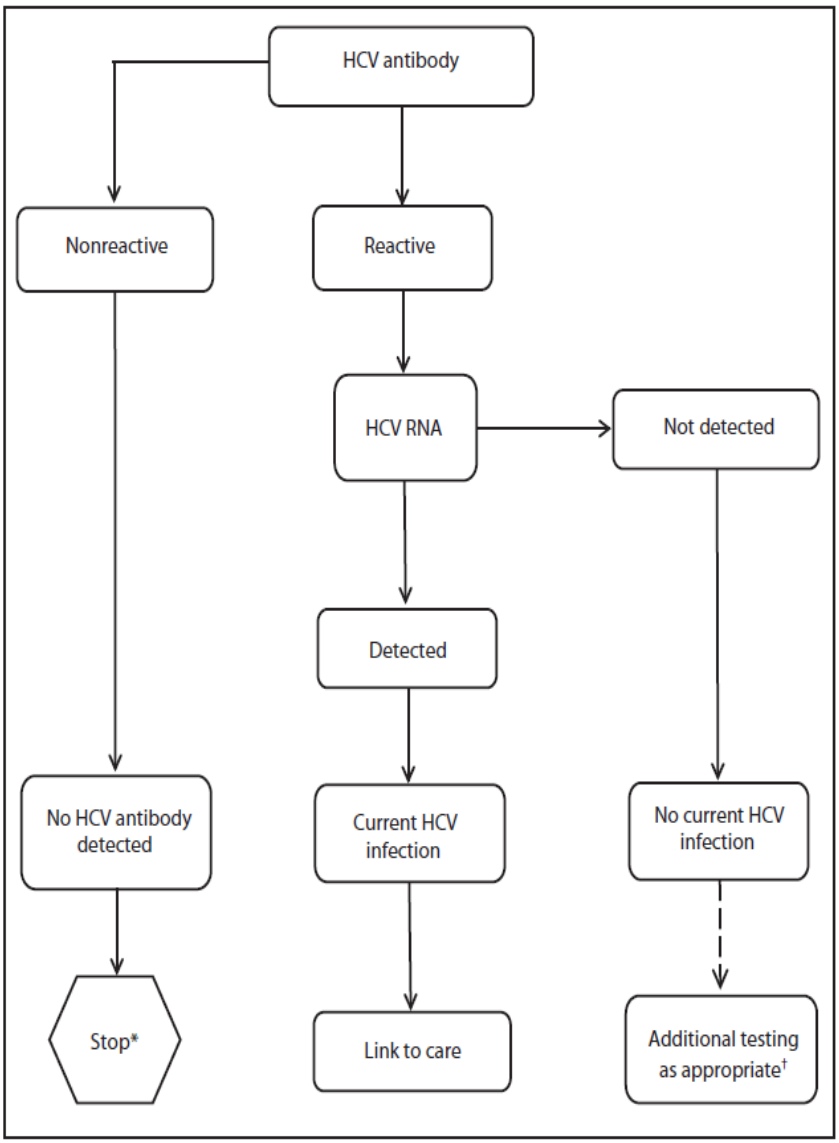
Testing and Linkage to Care Table 2. Measures Transmission of HCV

- Persons with HCV infection should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
- Persons should be counseled to stop using illicit drugs and enter substance abuse treatment. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment; use new sterile syringes and filters and disinfected cookers; clean the injection site with a new alcohol swab; and dispose of syringes and needles after one use in a safe, puncture-proof container.
- Persons with HCV infection should be advised not to donate blood and to discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- MSM with HIV infection and those with multiple sexual partners or sexually transmitted infections should be encouraged to use barrier precautions to prevent sexual transmission. Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

Testing and Linkage to Care Table 3: Common Barriers to HCV Treatment and Potential Strategies

Barrier	Strategy
Contraindications to treatment (eg, comorbidities, substance abuse, and psychiatric disorders)	▪ Counseling and education ▪ Referral to services (eg, psychiatry and opioid substitution therapy) ▪ Optimize treatment with simpler and less toxic regimens
Competing priority and loss to follow-up	▪ Conduct counseling and education ▪ Engage case managers and patient navigators (HIV model) ▪ Co-localize services (eg, primary care, medical homes, and drug treatment)
Long treatment duration and adverse effects	▪ Optimize treatment with simpler and better tolerated regimens ▪ Education and monitoring ▪ Directly observed therapy (tuberculosis model)
Lack of access to treatment (high cost, lack of insurance, geographic distance, and lack of availability of specialists)	▪ Leverage expansion of coverage through the Patient Protection and Affordable Care Act ▪ Participate in models of care involving close collaboration between primary care practitioners and specialists ▪ Pharmaceutical patient assistance programs ▪ Co-localize services (primary care, medical homes, drug treatment)
Lack of practitioner expertise	▪ Collaboration with specialists (eg, via Project ECHO-like models and telemedicine) ▪ Develop accessible and clear HCV treatment guidelines ▪ Develop electronic health record performance measures and clinical decision support tools (eg, pop-up reminders and standing orders)

Testing and Linkage to Care Figure 1. CDC Recommended Testing Sequence for Identifying Current HCV Infection



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Adapted from Centers for Disease Control and Prevention (CDC), 2013. (Centers for Disease Control and Prevention [CDC], 2013)

INITIAL TREATMENT OF HCV INFECTION IN PATIENTS STARTING TREATMENT

A summary of recommendations for initial treatment is found in the box.

This section provides guidance on the recommended initial treatments for persons with chronic HCV infection who are naive to HCV treatment or who have achieved an undetectable level of virus during a prior treatment course of PEG/RBV and relapsed (relapsers). Although PEG/RBV relapsers are being retreated, their treatment recommendations are presently the same as for persons being treated for the first time as described below. This section assumes that ***a decision to treat has been made*** and provides guidance regarding optimal treatment. In many instances, however, it may be advisable to delay treatment for some patients with documented early fibrosis stage (F 0-2), because waiting for future highly effective, pangenotypic, DAA combinations in IFN-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future update to this guidance.

The level of evidence available to inform the best treatment decisions for each patient varies, as does the strength of the recommendation, and is graded accordingly (see Methods Table 2). In addition, when treatment differs for a particular group, such as those infected with specific HCV genotypes, specific recommendations are given. A regimen is classified as either "Recommended" when it is favored for most patients or "Alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "Not Recommended." Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations of persons with HIV/HCV coinfection, compensated and decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), post-liver transplant HCV, and those with severe renal impairment or ESRD are addressed in other sections of the document.

As always, patients receiving antiviral therapy require careful pretreatment assessment for comborbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen.

I. Genotype 1

Recommended regimen for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level A

Sofosbuvir is a prodrug of a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase. The phase 3 NEUTRINO trial evaluated sofosbuvir (400 mg daily) in combination with PEG (2a) (180 µg by subcutaneous injection weekly) and weight-based RBV (1000 mg to 1200 mg daily) for 12 weeks in 291 treatment-naive patients with chronic HCV genotype 1 infection. (Lawitz, 2013b) The SVR12 for patients with genotype 1 infection was 89%. SVR12 did not differ substantially by baseline characteristic but was lower in patients with cirrhosis (80%) than in those without cirrhosis (92%). (Lawitz, 2013b)

Recommended regimen for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg) for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level B

COSMOS is an ongoing phase 2 clinical trial of sofosbuvir (400 mg daily) plus simeprevir (150 mg daily), a specific inhibitor of the HCV NS3/4A serine protease, with or without RBV for 12 or 24 weeks. (Jacobson, 2013b) The study enrolled 2 cohorts: cohort 1 included patients with a prior null response to PEG/RBV with Metavir fibrosis stage of 0 or 2 (n=80); Cohort 2 included patients who were either treatment-naive or had a prior null response with Metavir fibrosis stage of 3 or 4 (n=87). In cohort 1, the 12-week treatment groups, SVR12 was 96% and 93% in patients treated with or without RBV, respectively. The 24-week treatment groups had SVR12 of 79.3% and 93% in patients treated with or without RBV, respectively. No viral breakthrough was observed in cohort 1 during treatment, and 3

patients experienced viral relapse after stopping therapy. All 3 patients with viral relapse were infected with HCV genotype 1a and had the Q80K polymorphism.

Preliminary SVR4 results are available for cohort 2. The 12-week treatment duration group had 100% SVR in treatment-naive patients treated with or without RBV, and 100% and 93.3% in prior null responder patients treated with or without RBV, respectively. No viral breakthrough was observed during treatment; 1 patient infected with HCV genotype 1a/Q80K experienced viral relapse after stopping therapy. No SVR data are yet available from cohort 2, which received 24 weeks of treatment.

Among patients who had viral relapse, simeprevir (protease) resistance-associated variants have been observed; sofosbuvir (polymerase) resistance-associated variants have not been detected. Safety data have been presented for all 167 patients treated. The combination was well tolerated, with only 2.4% of patients prematurely discontinuing therapy due to adverse events. Data on the use of simeprevir in patients with hepatic impairment are not available at this time.

For patients infected with genotype 1a HCV, baseline resistance testing for the Q80K polymorphism may be considered. However, in contrast to using simeprevir to treat a genotype 1a HCV patient with PEG/RBV when the mutation markedly alters the probability of an SVR, the finding of the Q80K polymorphism does not preclude treatment with simeprevir and sofosbuvir, because the SVR rate was high in patients with genotype 1a/Q80K infection (SVR12 rate for cohort 1 was 86% [24 of 28 patients]; SVR4 rate for cohort 2 was 90% [10 of 11 patients]). To date, virologic failure has not been observed in patients in either cohort infected with HCV genotype 1b and with HCV genotype 1a in the absence of the Q80K polymorphism. Thus Q80K testing can be considered but is not strongly recommended.

This regimen should be considered only in those patients who require immediate treatment, because it is anticipated that safer and more effective IFN-free regimens will be available by 2015.

Alternative regimens for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 24 weeks is an acceptable regimen for IFN-eligible persons with either

1. *HCV genotype 1b or*
2. *HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment.*

Rating: Class IIa, Level A

Two randomized, placebo-controlled phase 3 trials evaluated the efficacy and safety of simeprevir (150 mg once daily) for 12 weeks plus PEG and weight-based RBV for a total of 24 weeks (RGT design found no advantage to extending PEG/RBV to 48 weeks). (Jacobson, 2013a); (Poordad, 2013)

In both studies, SVR24 rates were significantly higher among the simeprevir-containing arms (80% to 81%) than in the non-simeprevir-containing arms (50%). If the HCV RNA at week 4 of treatment is less than 25 IU/mL, therapy should be continued to week 24. If the HCV RNA is greater than 25 IU/mL at treatment week 4 or any treatment week thereafter, the regimen should be discontinued. In patients with HCV genotype 1a infection, the presence of a naturally occurring NS3-4A protease polymorphism (Q80K) prior to treatment was associated with a substantial reduction in SVR among patients treated with simeprevir. A statistically significant difference in SVR12 rates exists between simeprevir-treated persons who are infected with HCV genotype 1a but do not have the Q80K polymorphism and placebo-treated patients who likewise have no such polymorphism. This difference was noted in both the pooled treatment-naive studies and the relapser study (SVR rates of 84% versus 43%, respectively [treatment-naive study] and 78% versus 24%, respectively [relapse study]). The overall SVR in the subgroup of patients with baseline Q80K polymorphism was no better than that in the placebo group. In the United States, persons with genotype 1a HCV infection have a high prevalence of Q80K polymorphism. Because these persons may require alternative therapy, baseline testing for Q80K is recommended for all patients before treatment with the simeprevir plus PEG/RBV regimen is initiated.

For the simeprevir plus PEG/RBV treatment regimen, if the HCV RNA at week 4 of treatment is less than 25 IU/mL, therapy should be continued to week 24. If the HCV RNA is greater than 25 IU/mL at treatment week 4 or any treatment week thereafter, the regimen should be discontinued.

Alternative regimens for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is an acceptable regimen for IFN-ineligible persons with HCV genotype 1 infection, regardless of subtype; however, preliminary data suggest that this regimen may be less effective than daily sofosbuvir (400 mg) plus simeprevir (150 mg), particularly among patients with cirrhosis.

Rating: Class IIb, Level B

Sofosbuvir plus RBV was evaluated in 60 treatment-naive patients with HCV genotype 1 with unfavorable treatment characteristics (eg, African American race and advanced fibrosis). (Osinusi, 2013) In part 1 of the study, 10 participants with early to moderate liver fibrosis were treated with sofosbuvir (400 mg daily) plus weight-based RBV for 24 weeks. Nine participants (90%) achieved SVR24. In part 2, 50 participants with any stage of liver fibrosis were randomized 1:1 to receive 400 mg sofosbuvir with RBV either weight-based or low-dose (600 mg daily) for 24 weeks; SVR24 was 68% (17/25) in the weight-based group and 48% (12/25) in the low-dose group. The regimens used in part 2 of this study were well tolerated, with no discontinuations due to adverse events. Seven of the 13 participants (54%) with advanced liver fibrosis treated in this study relapsed, including all 4 with cirrhosis.

Several additional studies have evaluated the effectiveness of sofosbuvir in persons with HCV genotype 1. In the QUANTUM trial, 38 treatment-naive patients with HCV genotype 1 who did not have cirrhosis were assigned either 12 (n=19) or 24 (n=19) weeks of sofosbuvir (400 mg daily) and weight-based RBV. (Lalezari, 2013) Ten of 19 (53%) in the 12-week arm and 9 of 19 (47%) subjects in the 24-week arm achieved SVR12 (overall 50%). In the ELECTRON trial, 25 treatment-naive subjects with HCV genotype 1 who did not have cirrhosis received sofosbuvir plus RBV for 12 weeks. Twenty-one (84%) achieved SVR12. (Gane, 2013b) In the PHOTON-1 trial, 86 of 113 (76%) treatment-naive subjects with genotype 1 HCV/HIV coinfection achieved SVR12 with sofosbuvir plus RBV for 24 weeks. (Sulkowski, 2013c) Taken together, in a total of 211 subjects, the range of SVR for regimens incorporating sofosbuvir plus daily weight-based RBV (1000 mg to 1200 mg) for up to 24 weeks in treatment-naive persons with HCV genotype 1 was 50% to 84%, with an overall SVR of 72%. Sofosbuvir resistance-associated amino acid variants have not been detected among those patients treated with this combination who did not achieve SVR.

This regimen should be considered only in those patients who require immediate treatment. It is estimated that the FDA will approve safer and more effective IFN-free regimens by 2015.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 1.

- **PEG/RBV with or without telaprevir or boceprevir for 24 to 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

Although regimens of PEG/RBV plus telaprevir or boceprevir for 24 to 48 weeks using RGT are also FDA approved, they are markedly inferior to the preferred and alternative regimens. These regimens are associated with their higher rates of serious adverse events (eg, anemia and rash), longer treatment duration, high pill burden, numerous drug-drug interactions, frequency of dosing, intensity of monitoring for continuation and stopping of therapy, and the requirement to be taken with food or with high-fat meals.

PEG/RBV for 48 weeks for treatment-naive subjects with HCV genotype 1 has been superseded by treatments incorporating DAAs and should not be used.

II. Genotype 2

Recommended regimen for treatment-naive patients with HCV genotype 2, regardless of eligibility for IFN therapy:

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.

Rating: Class I, Level A

Sofosbuvir (400 mg daily) was combined with weight-based RBV (1000 mg to 1200 mg) to treat HCV genotype 2 treatment-naive patients across 3 clinical trials: FISSION, POSITRON, and VALENCE. (Lawitz, 2013b); (Jacobson, 2013c); (Zeuzem, 2013b) The FISSION study randomized patients to daily PEG/RBV (800 mg) for 24 weeks or sofosbuvir plus daily weight-based RBV (1000 mg to 1200 mg). (Lawitz, 2013b) The SVR was higher (94%) in patients who received sofosbuvir plus RBV compared with those who received PEG/RBV (78%) (52/67). Across all 3 trials, 201 of 214 (94%) patients with HCV genotype 2 achieved SVR with sofosbuvir plus RBV. Among patients who did not achieve SVR, sofosbuvir resistance-associated amino acid variants were not detected. (US FDA, 2013a)

Alternative Regimens for treatment-naive patients with genotype 2:

None

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 2.

- **PEG/RBV for 24 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir-, boceprevir-, or simeprevir-based regimens**

  Rating: Class III, Level A

PEG (2a) (180 µg weekly) or PEG (2b) (1.5 µg/kg weekly) plus RBV (800 mg daily) for 24 weeks was directly compared with sofosbuvir (400 mg daily) plus weight-based RBV (1000 mg to 1200 mg daily) in the FISSION trial. (Lawitz, 2013b) The SVR12 achieved with PEG/RBV was lower than that achieved with sofosbuvir/RBV overall (78% and 95%, respectively) and in the subgroups of patients with or without cirrhosis. Safety and tolerability of PEG/RBV was inferior to the profile observed with sofosbuvir and RBV, with greater frequency of reported adverse events and laboratory abnormalities as well as a higher rate of treatment due to adverse events. Further, the duration of therapy with PEG/RBV is 12 weeks longer than that of sofosbuvir plus RBV.

Due to their poor in vitro and in vivo activity, boceprevir and simeprevir should not be used as therapy for patients with HCV genotype 2 infection. Although telaprevir combined with PEG/RBV has antiviral activity against HCV genotype 2, (Foster, 2011) the additional side effects and longer duration of therapy do not support use of this regimen.

III. Genotype 3

Recommended regimen for treatment-naive patients with HCV genotype 3, regardless of eligibility for IFN therapy:

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 3 infection.

Rating: Class I, Level B

The VALENCE study assessed the efficacy and safety of sofosbuvir (400 mg daily) plus RBV for 24 weeks in 250 treatment-naive (42%) and treatment-experienced (58%) subjects with HCV genotype 3 infection. The overall SVR12 was 84% and was higher among treatment-naive than treatment-experienced patients (93% versus 77%, respectively). These results suggest higher response rates can be achieved with a 24-week duration of sofosbuvir plus RBV than those reported for the 12- or 16-week durations studied in the FISSION (Lawitz, 2013b) (12 weeks, SVR12: 63%), POSITRON, (Jacobson, 2013c) (12 weeks, SVR 12: 61%) and FUSION (12 weeks, SVR12: 30%, 16 weeks, SVR12: 62%) trials. The primary reason for the higher SVR with extended therapy among treatment-naive patients was a reduction in the relapse rate from 40% to 5%. In sub-analysis, response rates were similarly high among those with (n=45) and without (n=100) cirrhosis (92% and 93%, respectively).

Alternative regimens for treatment-naive patients with genotype 3 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 3.

Rating: Class IIa, Level A

The combination of sofosbuvir plus PEG/RBV has been evaluated in patients with genotype 3 infection. In 2 phase 2 clinical trials, PROTON and ELECTRON, 38 of 39 (97%) treatment-naive patients with genotype 3 infection achieved SVR with sofosbuvir plus PEG (4 to 12 weeks of therapy)/RBV. (Gane, 2013b) For many patients with genotype 3, the adverse effects and increased monitoring requirements of PEG make this less acceptable than the recommended regimen of sofosbuvir plus weight-based RBV.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 3.

- **PEG/RBV for 24 to 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir-, boceprevir-, or simeprevir-based regimens should not be used for patients with genotype 3 HCV infection.**

  Rating: Class III, Level A

Although the combination of PEG/RBV is an FDA-approved regimen for HCV genotype 3, its less acceptable adverse effect profile, requirement for more intensive monitoring, and overall lower efficacy make it less desirable than the recommended regimen.

Because of their limited in vitro and in vivo activity against genotype 3, boceprevir, telaprevir, and simeprevir should not be used as therapy for patients with HCV genotype 3 infection.

IV. Genotype 4

Few data are available to help guide decision-making in patients infected with HCV genotype 4. Nonetheless, for those patients for whom immediate treatment is required, the following recommendations have been drawn from available data.

Recommended regimen for treatment-naive patients with HCV genotype 4 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIa, Level B

In the Phase 3 NEUTRINO trial, (Lawitz, 2013b) 28 treatment-naive patients with HCV genotype 4 infection were treated with sofosbuvir (400 mg daily) plus PEG (2a) (180 µg weekly) and weight-based RBV (1000 mg 1200 mg once daily) for 12 weeks. Of the 28 patients with genotype 4, 27 (96%) achieved SVR12. The one patient who did not achieve SVR had cirrhosis and relapsed after therapy. The adverse event profile was similar to that seen with PEG/RBV therapy.

Recommended regimen for treatment-naive patients with genotype 4 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for IFN-ineligible patients with HCV genotype 4 infection.

Rating: Class IIb, Level B

In a small study of Egyptian patients in the United States treated with sofosbuvir plus weight-based RBV (1000 mg to 1200 mg), SVR12 was achieved in 11 of 14 (79%) treatment-naive patients treated for 12 weeks; SVR24 was achieved in 100% of the 14 treatment-naive patients treated for 24 weeks. (Ruane, 2013)

Alternative regimens for treatment-naive patients with HCV genotype 4 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 24 to 48 weeks is an alternative regimen for IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIb, Level B

A Phase 3 trial in patients with HCV genotype 4 is currently under way. This trial compares PEG and weight-based RBV (1000 mg to 1200 mg) for 48 weeks with a 12-week regimen of simeprevir 150 mg once daily plus PEG and weight-based RBV (1000 mg to 1200 mg) followed by an additional 12 or 36 weeks of PEG/RBV alone. (Moreno, 2013) In another study, the RESTORE trial, an RGT approach is used in place of the simeprevir arm. Patients who have HCV RNA below 25 IU/mL at week 4 and undetectable HCV RNA by week 12 continue PEG/RBV for an additional 12 weeks, and those who do not achieve this response continue PEG/RBV for an additional 36 weeks (total 48 weeks of therapy). The study has enrolled 107 patients, of whom 35 are treatment-naive, including 2 with cirrhosis. To date, 10 of 11 patients (91%) who met criteria for shortened therapy have achieved SVR4, and 3 of 3 have achieved SVR12. To date, therapy has failed in 4 patients: 3 had detectable virus at the end of treatment and 1 experienced virologic relapse. Anemia was reported in 8.4% and hyperbilirubinemia in 1.9% of all study participants (n=107) (including treatment-experienced patients). Four serious adverse events were attributed to simeprevir. No episodes of rash were reported. (Moreno, 2013)

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 4.

- **PEG/RBV for 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir-based regimens**

  Rating: Class III, Level A

PEG/RBV for 48 weeks was the previously recommended regimen for patients with HCV genotype 4. The addition of sofosbuvir (400 mg daily) to PEG/RBV increases response rates and markedly shortens therapy with no apparent additional adverse effects. The addition of simeprevir to PEG/RBV increases response rates with a minimal increase in adverse events and can shorten therapy to 24 weeks.

Because of their limited in vitro and in vivo activity against genotype 4, boceprevir or telaprevir should not be used as therapy for patients with HCV genotype 4 infection.

V. Genotype 5 or 6

Few data are available to help guide decision-making in patients infected with HCV genotype 5 or 6. Nonetheless, for those patients for whom immediate treatment is required, the following recommendations have been drawn from available data. No data are available to support the use of a non-PEG containing regimen for patients with HCV genotype 5 or 6 infection.

Recommended regimen for treatment-naive patients with HCV genotype 5 or 6.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level B

In the Phase 3 NEUTRINO trial (Lawitz, 2013b), treatment-naive patients with genotypes 1 (n=291), 4 (n=28), 5 (n=1), and 6 (n=6) were treated with sofosbuvir (400 mg daily) plus PEG (2a) (180 µg per week) and weight-based RBV (1000 mg 1200 mg once daily) for 12 weeks. All 6 patients with HCV genotype 6 and the 1 patient with genotype 5 achieved SVR12. The adverse event profile in these patients and in the larger study population was similar to that seen with PEG/RBV therapy.

Alternative regimens for treatment-naive patients with HCV genotype 5 or 6.

Daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 48 weeks is an acceptable regimen for persons infected with HCV genotype 5 or 6.

Rating: Class IIb, Level A

PEG/RBV for 48 weeks was the previously recommended regimen for patients infected with HCV genotype 5 or 6. Sofosbuvir has activity against genotypes 5 and 6, and when combined with PEG/RBV for 12 weeks led to SVR in the 6 patients in whom it was studied. (Lawitz, 2013b) The addition of sofosbuvir (400 mg daily) to PEG/RBV shortens duration of therapy with no apparent additional adverse effects and likely substantially increases response rates.

The following regimens are NOT recommended for treatment-naive patients with genotype 5 or 6 HCV.

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir-based regimens**

  Rating: Class III, Level A

Because of their limited activity in vitro and in vivo against genotypes 5 and 6, boceprevir or telaprevir should not be used as therapy for patients with genotype 5 or 6 HCV infection.

Initial Treatment Box. Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection or Who Experienced Relapse after Prior PEG/RBV Therapy, by HCV Genotype

Genotype	Recommended	Alternative	NOT Recommended
1	**IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + SMV ± RBV x 12 weeks	**IFN eligible:** SMV x 12 weeks + PEG/RBV x 24 weeks* **IFN ineligible:** SOF + RBV x 24 weeks	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	None	PEG/RBV x 24 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV x 24-48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
4	**IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC
5 or 6	SOF + PEG/RBV x 12 weeks	PEG/RBV x 48 weeks	Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC

For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.

RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

A summary of recommendations for retreatment is found in the box.

This section provides guidance on the retreatment of a person with chronic HCV infection in whom prior therapy has failed. In general, treatment responses of patients achieving an undetectable level of virus during a prior treatment course who relapse following cessation of therapy (**relapser**) are similar to those of treatment-naive persons (see Initial Treatment). Treatment responses are generally lower in prior **non-responders**, which includes null responders (those in whom serum HCV RNA levels declined less than 2 $\log_{10}$ IU/mL by week 12 during a prior treatment course) and partial responders (those with a ≥ 2 $\log_{10}$ IU/mL response whose virus remained detectable up to 24 weeks or the end of treatment). This section assumes that ***a decision to treat has been made*** and advises on the optimal treatment. In many instances, however, it may be advisable to delay treatment for some patients with documented early fibrosis stage (F 0-2), because waiting for future highly effective, pangenotypic, combinations in IFN-free regimens may be prudent. Potential advantages of waiting to begin to treatment will be provided in a future update to this guidance.

The level of the evidence supporting the best treatment for each patient and the corresponding confidence in the recommendation varies as does the strength of the recommendation, and is graded in the same manner as the section on initial treatment of treatment-naive patients (Methods Table 2). In addition, when treatment differs for a particular group (eg, those infected with various genotypes) specific recommendations are given. Regimens are classified as "Recommended" when it is favored for most patients or "Alternative" when it might be optimal in a particular subset of patients in that category. When a treatment is clearly inferior or should not be used, it is classified as "Not Recommended."

As always, patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen.

I. Genotype 1

Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) nonresponder patients:

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility

Rating: Class IIa, Level B

COSMOS is a phase 2a randomized trial in which participants received sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily) with or without weight-based RBV (1000 mg to 1200 mg daily) for 12 or 24 weeks (Jacobson, 2013b). Of the 80 null responders with a Metavir fibrosis stage of 2 or less included in this trial, 79% to 96% achieved SVR (79%-96% in RBV-containing arms and 93% in both RBV-free arms). Among those null responders with a Metavir fibrosis stage of 3 or 4 (n=47) who received 12 weeks of sofosbuvir and simeprevir, SVR4 was observed in 14 (93%) of 15 patients in the ribavirin-containing arm and 100% (all 7 participants) in the RBV-free arm. Although benefit from RBV is not apparent from these preliminary results, it cannot be excluded before availability of SVR12 data. Post-treatment results are not yet available for the 24-week arms. Excluding nonvirologic failures, patients with HCV genotype 1a with Q80K mutations had slightly lower numeric response rates (fibrosis stage 0-2: SVR12=89% [n=27]; fibrosis stage 3 or 4: SVR4=91% [n=11]) than genotype 1a patients without Q80K and genotype 1b (fibrosis stage 2: SVR12 100%, n=47; fibrosis stage 3 or 4: SVR4=100% [n=29]). However, because the study was not powered to assess this comparison, insufficient evidence exists on the role of testing for the Q80K mutation at this time. These regimens were well tolerated, although adverse events (eg, anemia and hyperbilirubinemia) were seen more often in patients on RBV-containing regimens. (Jacobson, 2013b)

The safety and efficacy of simeprevir have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The uncertain impact of cholestasis and the occasional association of SMV with elevated transaminases create potential for drug accumulation or impaired hepatic function during SMV use. Clinical trials with SMV have been limited to patients with compensated disease who have CTP class A, total bilirubin of 1.5 x ULN or lower, and transaminases 10 x ULN or lower. For these reasons, simeprevir use should be limited to patients with compensated liver disease. Use of simeprevir is not recommended in patients with moderate to severe hepatic impairment. The combination of PEG/RBV is contraindicated in patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Alternative regimen for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 to 24 weeks is an alternative for retreatment of IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C

NEUTRINO is an open-label, single-arm trial that evaluated 12 weeks of sofosbuvir plus PEG/RBV in treatment-naive subjects with HCV genotypes 1, 4, 5, or 6; 89% had HCV genotype 1, and 17% had cirrhosis. The SVR was 89% (261 of 292) and was somewhat lower in patients with genotype 1b than 1a (82% and 92%, respectively) and those with cirrhosis versus those without (80% versus 92%, respectively). (Lawitz, 2013a) Although treatment-experienced subjects were not included in this study, FDA estimates that the response rate in such patients would approximate the observed response rate in those NEUTRINO subjects with baseline factors traditionally associated with a lower response to IFN-based treatment. (US FDA, 2013a) In the NEUTRINO trial, SVR rate was 71% among participants with HCV genotype 1 with IL28B non-C/C alleles, high HCV RNA levels, and METAVIR 1 fibrosis stage F3 or F4 (37 of 52 patients). (Gilead Sciences, 2013; Solvadi package insert)

Alternative regimen for PEG/RBV (without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) and weekly PEG for 48 weeks is an alternative for IFN-eligible persons with HCV genotype 1 infection. (All patients with cirrhosis who are receiving simeprevir should have well compensated liver disease.)

Rating: Class IIa, Level A

Simeprevir was combined with PEG/RBV in patients who had previously failed to respond to PEG/RBV dual therapy in the Phase 2b ASPIRE trial. (Zeuzem, 2013a); (Janssen Therapeutics, 2013) (www.fda.gov; package insert). SVR24 after 48 weeks of triple therapy in the simeprevir 150 mg/day arm was 65% in patients with a previous partial response (n=23) and 53% in patients with a prior null response (n=17). Patients with HCV genotype 1a infection had inferior response rates compared with those with genotype 1b (SVR24: 47% vs 77% in patients with a partial response and 41% vs 47% in patients with a null response, respectively). Despite lower SVR in patients with HCV genotype 1a infection, SVR rates were similar with and without the presence of the Q80K mutations at baseline. SVR rates in patients with advanced fibrosis (METAVIR stage F3 or F4) treated with simeprevir (150 mg daily) plus PEG/RBV for 48 weeks were 59% in patients with a partial response (n=33) and 35% in patients with a null response (n=34). Safety in patients exposed to simeprevir was similar to that of persons in the placebo arms; however, there was a higher incidence of hyperbilirubinemia (8%) and photosensitivity/rash (5%). (Zeuzem, 2013a)

The safety and efficacy of simeprevir have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The uncertain impact of cholestasis and the occasional association of simeprevir with elevated transaminases pose potential for impaired hepatic function during simeprevir use. Clinical trials with simeprevir have been limited to patients with compensated disease who have CTP class A, total bilirubin level of 1.5 x ULN or lower, and transaminase level of 10 x ULN or lower. For these reasons, simeprevir use should be limited to patients with compensated liver disease. Use of simeprevir is not recommended in patients with moderate to severe hepatic impairment. Use of the drug in this population is not recommended at this time. The combination of PEG/RBV is contraindicated in patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

The following regimens are NOT recommended for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1:

- **PEG/RBV with or without telaprevir or boceprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

For nonresponder patients with genotype 1 and a history of decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), treatment is not indicated because of the risks of PEG and boceprevir and telaprevir in this population.

Triple therapy with boceprevir plus PEG/RBV for 48 weeks may result in SVR for up to 52% of PEG/RBV partial responders (RESPOND 2; (Bacon, 2011)) and 38% of null responders (PROVIDE; (Di Bisceglie, 2013)). Similarly, telaprevir plus PEG/RBV resulted in SVR24 of 54% to 59% among partial responders and an SVR24 of 29% to 33% among null responders (REALIZE; (Zeuzem, 2011)). Due to the relatively poor efficacy, prolonged duration of therapy (48 weeks), and poor tolerability, these regimens are no longer recommended.

Monotherapy with PEG, RBV, or any of the available DAAs is ineffective; further, DAA monotherapy leads to rapid selection of resistant variants.

Patients with advanced liver disease are at increased risk for sepsis, worsening decompensation, and death when treated with dual or triple IFN-based therapy. (Crippin, 2002); (Coilly, 2014) Simeprevir is primarily metabolized by the liver and should not be used in patients with advanced cirrhosis (CTP B or C), as the AUC is increased 2.4- to 5.2-fold. (Janssen Therapeutics, 2013) (Olysio package insert, Janssen).

II. Genotype 2

Recommended regimen for genotype 2 PEG/RBV nonresponders.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 2 infection. (Patients with cirrhosis may benefit by extension of treatment to 16 weeks.)

Rating: Class I, Level A

High SVR12 rates have been demonstrated in non-cirrhotic genotype 2 treatment-experienced patients who received 12 weeks of sofosbuvir plus RBV. Limited data are available in cirrhotic genotype 2 treatment experienced patients; however, in the FUSION study, numerically higher SVR12 rates were seen with extension of therapy from 12 weeks (60%) to 16 weeks (78%). (Jacobson, 2013b) In contrast, the VALENCE trial found high SVR12 rates among HCV genotype 2-infected persons with cirrhosis after only 12 weeks of sofosbuvir plus RBV (88%). (Zeuzem, 2013b) Thus, at this time definitive recommendations on the appropriate duration of sofosbuvir and RBV for treatment-experienced, HCV genotype 2-infected persons with cirrhosis cannot be made. The decision to extend therapy to 16 weeks should be made on a case-by-case basis.

Alternative regimen for PEG/RBV nonresponder patients with HCV genotype 2 infection who are eligible to receive IFN.

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 2 infection.

Rating: Class IIa Level B

Recognizing the potential limitations of sofosbuvir plus RBV in harder-to-treat genotype 2 nonresponders, particularly those with cirrhosis, combination therapy with PEG has been studied. The LONESTAR-2 trial (an open-label, single site, single-arm phase 2 trial) evaluated PEG (180 µg weekly), sofosbuvir (400 mg daily), and weight-based RBV (1000 mg to 1200 mg daily in 2 divided doses for 12 weeks) in treatment-experienced patients with HCV genotype 2 or 3. Cirrhosis was present at baseline in 61% of patients. SVR12 was achieved in 22 (96%) of 23 persons with genotype 2 HCV infection. For patients with and without cirrhosis, SVR occurred in 13 (93%) of 14 and 9 (100%) of 9, respectively. Despite the limitations of this small study (and accounting for the potential challenges inherent with IFN therapy), combination PEG plus sofosbuvir and RBV is an alternative 12-week regimen for genotype 2-infected patients with cirrhosis.

The following regimens are NOT recommended for nonresponder patients with HCV genotype 2.

- **PEG/RBV with or without telaprevir, boceprevir or simeprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

No HCV protease inhibitors have been approved or are indicated for the treatment of genotype 2 infection. Although PEG/RBV has been the mainstay of treatment of genotype 2, it requires a longer duration of therapy, is less efficacious, and has more adverse effects than the regimen recommended above.

III. Genotype 3

Recommended regimen for HCV genotype 3 PEG/RBV nonresponders.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for retreatment of HCV genotype 3 infection.

Rating: Class IIa, Level A

The phase 3 FUSION trial compared 12 weeks (n=103) with 16 weeks (n=98) of daily sofosbuvir (400 mg) and weight-based RBV (1000 mg to 1200 mg) in genotype 2 or 3 HCV-infected patients in whom previous PEG/RBV therapy had failed. Of patients, 63% had genotype 3; 34% of all patients had cirrhosis. Because persons who had experienced prior relapses to IFN-based therapy accounted for 75% of patients, the number of patients with a prior nonresponse in the study was limited. The SVR rate for genotype 3 patients in the 12-week arm was 30% (19% among patients with cirrhosis and 37% among those without cirrhosis). Extending therapy to 16 weeks increased the SVR rate among genotype 3 patients to 62% (61% among patients with and 63% in those without cirrhosis).

Based on results from FUSION, the phase 3 multicenter, randomized placebo-controlled VALENCE trial was amended to evaluate the effect of extending sofosbuvir plus RBV therapy to 24 weeks in all patients with HCV genotype 3. As with the FUSION study, most (65%) treatment-experienced patients had relapsed. The SVR12 rates after 24 weeks of therapy for treatment-experienced patients with genotype 3 was 79% (60% among patients with and 87% in those without cirrhosis). The increased efficacy with 24 weeks of sofosbuvir plus RBV therapy across all fibrosis stages combined with a favorable safety and tolerability profile supports the recommendation to use 24 weeks of sofosbuvir plus RBV in all genotype 3 patients despite the minimal number of patients studied to date. The response rate for HCV genotype 3-infected patients with cirrhosis treated for 24 weeks in the VALENCE trial (60%) was similar to that observed after 16 weeks of treatment in the FUSION trial (61%). Although longer treatment duration with a well-tolerated regimen may potentially be more successful in these more difficult-to-treat patients, data remain limited. Either duration of treatment is considered acceptable at this time (see below).

Alternate regimen for HCV genotype 3 PEG/RBV nonresponder patients who are eligible to receive IFN.

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 3 infection.

Rating: Class IIa Level B

Choice of specific regimen may be influenced by previous or anticipated tolerance to PEG or the presence of advanced fibrosis or cirrhosis. For most patients, the ease of administration and tolerability of sofosbuvir plus RBV will outweigh any potential benefit associated with the addition of PEG. However, for HCV genotype 3-infected patients who have cirrhosis, responses to sofosbuvir and RBV alone for 24 weeks were suboptimal.

In the LONESTAR-2 study, adding 12 weeks of PEG to the sofosbuvir and RBV regimen resulted in numerically higher response rates among persons with HCV genotype 3 than those obtained with sofosbuvir and RBV for 24 weeks. Of HCV genotype 3-infected patients with and without cirrhosis, 10 (83%) of 12 achieved SVR. Given the limited number of patients in this demographic in both the VALENCE and LONESTAR-2 studies, these differences in response rates should be interpreted with caution.

The following regimens are NOT recommended for nonresponder patients with HCV genotype 3 infection.

- **PEG/RBV with or without telaprevir, boceprevir or simeprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

No HCV protease inhibitors have been approved or are indicated for the treatment of genotype 3 HCV infection. Although PEG/RBV has been the mainstay of treatment of genotype 3 HCV, it is less efficacious and has more adverse effects than the recommended regimens.

IV. Genotypes 4, 5 and 6

Recommended regimen for HCV genotype 4, PEG/RBV nonresponder patients.

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIa, Level C

Alternate regimen for HCV genotype 4, PEG/RBV nonresponder patients.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for retreatment of HCV genotype 4 infection.

Rating: Class IIa, Level B

The following regimens are NOT recommended for nonresponder patients with genotype 4 HCV infection.

- **PEG/RBV with or without telaprevir or boceprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

Recommended regimen for HCV genotype 5 or 6, PEG/RBV nonresponder patients.

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level C

Alternate regimen for PEG/RBV nonresponder patients with HCV genotype 5 or 6.

None

The following regimens are NOT recommended for nonresponder patients with HCV genotype 5 or 6.

- **PEG/RBV with or without telaprevir or boceprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

In the NEUTRINO trial, high SVR rates were seen in small numbers of treatment-naive patients with HCV genotypes 4, 5, and 6 treated with sofosbuvir plus PEG/RBV for 12 weeks (genotype 4: n=28, SVR=96%; genotype 5: n=1, SVR=100%; and genotype 6: n=6, SVR=100%). (Lawitz, 2013a) In a pilot study of treatment-experienced HCV genotype 4 patients of Egyptian ancestry, SVR12 was 59% in patients treated with sofosbuvir plus RBV for 12 weeks; SVR4 was 93% in patients treated for 24 weeks. In this cohort, 24% to 27% of patients had cirrhosis. (Ruane, 2013) The only available data with simeprevir for treatment-experienced patients with genotype 4 come from the ongoing RESTORE trial, in which patients (n=50) are receiving treatment with daily simeprevir 150 mg for 12 weeks plus PEG/RBV for a total of 48 weeks (10 prior partial responders, 40 prior null responders). Interim analysis revealed a 40% to 49% RVR rate using this regimen. Final SVR results are pending. (Moreno, 2013) Given the relative paucity of data, expert consultation is needed to determine optimal duration of therapy in patients with genotype 4, 5, or 6 treated with sofosbuvir.

Retreatment Box. Recommendations for Patients in Whom Previous PEG/RBV Treatment Has Failed†

Genotype	Recommended	Alternative	NOT Recommended
Patients in whom previous PEG/RBV has failed*			
1	SOF + SMV ± RBV x 12 weeks	SOF x 12 weeks + PEG/RBV 12 weeks SMV x 12 weeks + PEG/RBV x 24 weeks**	PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a direct-acting antiviral agent Do not treat decompensated cirrhosis with PEG
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV ± any current protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
4	SOF x 12 weeks + PEG/RBV 12 weeks SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
5 or 6	SOF x 12 weeks + PEG/RBV 12 weeks	SOF + RBV x 24 weeks	PEG/RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
Patients in whom previous treatment with PEG/RBV plus either telaprevir or boceprevir has failed †† †††***			
1a	SOF x 12 weeks + PEG/RBV x 24 weeks	SOF + RBV x 24 weeks	PEG/RBV ± telaprevir or boceprevir or SMV
1b	SOF x 12 weeks + PEG/RBV x 12-24 weeks	SOF + RBV x 24 weeks	Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV

*Non-responder is defined as partial or null response to treatment with PEG/RBV. Relapse to prior therapy should be treated the same as treatment-naive (see Initial Treatment section)

**For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present

*** Non-responder is defined as partial or null response to treatment with PEG/RBV plus telaprevir or boceprevir. Relapse to prior therapy should be treated the same as treatment naive (see Initial Treatment section)

† Consideration should be given to postponing treatment, pending release of new drugs for patients with limited (F 0-2) hepatic fibrosis

†† A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure not provided due to potential risk of preexistant resistance to protease inhibitor treatment.

††† Given the lack of prior approval PI therapy for genotypes 2, 3, 4, 5, 6, and the lack of sufficient data, no recommendations are given for these genotype at this time

UNIQUE PATIENT POPULATIONS

1. Patients with HIV/HCV Coinfection

The summary of recommendations for HIV-coinfected patients is in the Unique Patient Populations: HIV/HCV Coinfection Box.

Recommended regimen(s) for treatment-naive and prior relapser HIV/HCV-coinfected patients with genotype 1 infection who are eligible to receive IFN:

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.**

  Rating: Class I, Level B

Recommended regimen(s) for treatment-naive and prior relapser HIV/HCV-coinfected patients with genotype 1 who are ineligible or unwilling to receive IFN.

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is recommended for treatment-naive HIV/HCV-coinfected patients with HCV genotype 1 infection.**

  Rating: Class I, Level B

- **Sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for treatment-naive and prior PEG/RBV relapser HIV/HCV-coinfected patients with genotype 1 infection. Simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.**

  Rating: Class IIa Level C

Recommended regimen(s) for treatment-experienced patients with HCV genotype 1 with a history of PEG/RBV nonresponse, regardless of IFN eligibility

- **Sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for prior PEG/RBV nonresponder, HIV/HCV-coinfected patients with genotype 1 infection. Simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.**

  Rating: Class IIa, Level C

Recommended regimen(s) for treatment-experienced patients with HCV genotype 1 with a history of PEG/RBV plus telaprevir or boceprevir nonresponse

- **Treat as recommended for HCV-monoinfected individuals.**

Recommended regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with genotype 2 and 3 infection

- **Use the same regimens as is recommended for persons with HCV monoinfection; specifically:**
  - *For patients with genotype 2 infection: sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for treatment-naive and treatment-experienced HIV/HCV-coinfected patients. Patients who are prior nonresponders and have cirrhosis may benefit by extension of treatment to 16 weeks.*

    Rating: Class I, Level B
  - *For patients with genotype 3 infection: sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is recommended for treatment-naive and treatment-experienced HIV/HCV-coinfected patients.*

    Rating: Class I, Level B

Recommended regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with genotype 4, 5, or 6 HCV:

- **Treat as recommended for persons with HCV monoinfection.**

HIV/HCV coinfection results in increased liver-related morbidity and mortality, non-hepatic organ dysfunction, and overall mortality. Even in the potent antiretroviral era, HIV infection remains independently associated with advanced liver fibrosis and cirrhosis in patients with HCV coinfection. (Thein, 2008); (de Ledinghen, 2008); (Fierer, 2013) Similar to HCV-monoinfected patients, HIV/HCV-coinfected patients cured with PEG/RBV have lower rates of hepatic decompensation, hepatocellular carcinoma, and liver related mortality. (Berenguer, 2009); (Limketkai, 2012); (Mira, 2013) Uptake of HCV therapy is limited in the HIV/HCV-coinfected population due to historically lower response rates, patient comorbidities, patient and practitioner perception, and the adverse events associated with IFN-based therapy. (Mehta, 2006); (Thomas, 2008) Due to the special population designation, the first 2 approved DAAs, telaprevir and boceprevir, remain off label for use in HIV/HCV-coinfected patients, further limiting access to treatment in this population. With the availability of the DAAs sofosbuvir and simeprevir, a milestone has been reached in HIV/HCV coinfected patients. Treatment of HIV/HCV-coinfected patients requires awareness and attention to the complex drug interactions that can occur between DAA and HIV antiretroviral medications.

Pharmacokinetics and Drug Interactions

Sofosbuvir is not metabolized by the hepatic P450 enzyme complex and is a substrate (but not an inhibitor) of drug transporters, p-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). It is not a substrate of OATP. Drug interaction studies with antiretroviral drugs (ie, efavirenz, tenofovir, emtricitabine, rilpivirine, darunavir/ritonavir, and raltegravir) in non-infected persons identified no clinically significant interactions (Kirby, 2013) making sofosbuvir an ideal therapy for patients with HIV/HCV coinfection. Sofosbuvir is not recommended for use with tipranavir because of the potential of this antiretroviral drug to induce P-gp (see package insert).

Simeprevir is metabolized primarily by cytochrome P450 3A4 (CYP3A4) and therefore is susceptible to drug interactions with inhibitors and inducers of the enzyme. Simeprevir is also an inhibitor of the OATP and P-gp transporters leading to additional drug interaction concerns. Drug interaction studies with antiretroviral drugs in non-infected volunteers suggested no substantial interactions with tenofovir, rilpivirine, or raltegravir; however, simeprevir concentrations were substantially decreased when dosed with efavirenz and substantially increased when dosed with darunavir/ritonavir, resulting in their exclusion from the Phase III C212 clinical trial investigating simeprevir in combination with PEG/RBV in patients with HIV/HCV coinfection. (Ouwerkerk-Mahadevan, 2012)

Ribavirin has the potential for dangerous drug interactions with didanosine resulting in mitochondrial toxicity with hepatomegaly/steatosis, pancreatitis, and lactic acidosis; thus the concomitant administration of these 2 drugs is contraindicated. (Fleischer, 2004) The combined use of RBV and zidovudine has been reported to increase the rates of anemia and the need for RBV dose reduction, and thus zidovudine is not recommended for use with RBV. (Alvarez, 2006)

Sofosbuvir (400 mg once daily) as part of a triple-therapy regimen with PEG (180 µg weekly) and weight-based RBV (1000 mg to 1200 mg daily given in divided doses) is safe and efficacious in patients with HCV monoinfection, with an overall SVR12 of 89% in HCV genotype 1 patients. The P7977-1910 study was a single-center, single-arm trial (N=23) investigating this same 12-week triple therapy regimen in HIV-infected patients coinfected with HCV genotypes 1, 2 3, or 4. (Rodriguez-Torres, 2013) Allowable antiretrovirals included either efavirenz, atazanavir/ritonavir, darunavir/ritonavir, raltegravir, or rilpivirine in combination with tenofovir/emtricitabine. Of patients with HCV genotype 1 (N=19), 89% achieved SVR12; 2 patients discontinued the study early due to adverse events (ie, anemia and altered mood). This regimen is therefore recommended for persons with HIV/HCV genotype 1 coinfection who are eligible to receive IFN and are either treatment-naive or have had prior PEG/RBV relapse.

The Phase III PHOTON-1 study enrolled 182 treatment-naive patients with HIV/HCV coinfection (n=114 with genotype 1; n=26 with genotype 2; n=42 with genotype 3) in a single-arm clinical trial investigating sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily given in divided doses) for 24 (genotype 1) or 12 (genotypes 2 and 3) weeks. (Sulkowski, 2013c) The population had well-controlled HIV with mean CD4 counts of 559 to 636 cells/µL. The same ARVs were allowed as those in the P7977-1910 study. Of participants, 90% completed treatment and 3% discontinued treatment due to adverse events. SVR12 was achieved in 76%, 88%, and 67% of participants with HCV genotypes 1, 2, and 3, respectively. For the combination of sofosbuvir plus RBV, genotype 1b subtype was a predictor of poorer response. Cirrhosis and African American race also exhibited trends toward lower SVR12. Based on the potential for lower response in HIV/HCV-coinfected patients with cirrhosis, the use of sofosbuvir plus PEG/RBV should be considered over sofosbuvir plus RBV. This regimen is otherwise recommended for HIV/HCV genotype 1-coinfected patients who are treatment naive or have relapsed after receipt of PEG/RBV and are ineligible for IFN.

The combination of simeprevir plus sofosbuvir with or without RBV has been studied in the phase II COSMOS trial in patients with HCV monoinfection. (Jacobson, 2013b) This study is the basis for the recommendation supporting the use of this all-oral combination as an alternative regimen for patients with HCV monoinfection who cannot tolerate the recommended regimens. Although sofosbuvir plus simeprevir has been used anecdotally in patients with HIV/HCV coinfection, this drug combination has never been studied in this population. Despite the absence of data, this regimen may be considered for the treatment of HCV genotype 1 infection in patients with HIV infection who are not eligible for IFN and who are receiving antiretroviral therapy that may be coadministered with simeprevir (ie, raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir).

Similarly, no data exist for the combination of sofosbuvir plus simeprevir for the (re)treatment of HCV infection in HIV-infected patients. However, preliminary results obtained in HCV-monoinfected patients, including those with prior treatment failure and advanced fibrosis, support the expectation that this regimen will be highly effective in coinfected patients receiving compatible antiretroviral therapy as

described above (see Retreatment of HCV Monoinfected Patients). (Jacobson, 2013b) Given the lack of clinical data in this population, it may be prudent to reserve this regimen for the treatment of persons with advanced fibrosis in whom a delay of therapy may lead to adverse clinical outcomes.

No data with sofosbuvir currently exist to guide retreatment recommendations for coinfected patients with HCV genotype 2 or 3 HCV infection. The ongoing PHOTON-1 study enrolled 41 treatment-experienced patients coinfected with HCV genotype 2 or 3, receiving sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily given in divided doses) for 24 weeks. (Sulkowski, 2013b) Results are expected in early 2014. In the absence of data, current recommendations for the retreatment of HIV patients coinfected with HCV genotype 2 or 3 are the same as those for HCV-monoinfected patients. Data also are lacking regarding use of sofosbuvir among patients coinfected with HCV genotype 4, 5, or 6 and HIV. Similarly, with no current data on the use of sofosbuvir in patients with genotype 4, 5, or 6 HCV and HIV coinfection, but given evidence of safety and efficacy of sofosbuvir-based regimens in this population, the recommended regimens for treatment in treatment-naive and treatment-experienced patients with HIV/HCV coinfection are the same as those for HCV-monoinfected patients.

Alternative regimen(s) for treatment-naive or treatment-experienced (prior PEG/RBV relapse) HIV/HCV- coinfected patients with genotype 1 who are eligible to receive IFN

- **Simeprevir (150 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 24 weeks (for treatment-naive and treatment-experienced with prior relapse to PEG/RBV) is an acceptable regimen for IFN-eligible HIV/HCV-coinfected persons with either (1) HCV genotype 1b or (2) HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment. Simeprevir can only be used with the following antiretroviral drugs: raltegravir, rilpivirine, maraviroc, enfuvirtide tenofovir, emtricitabine, lamivudine, and abacavir.**

  Rating: Class IIa, Level B

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponders) HIV/HCV-coinfected patients with genotype 1 who are eligible for IFN

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.**

  Rating: Class IIb, Level C

Alternative regimen(s) for treatment-naive and PEG/RBV relapser HIV/HCV-coinfected patients with genotype 1 who are ineligible or unwilling to receive IFN.

- **None**

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponder) HIV/HCV-coinfected patients with genotype 1 who are ineligible to receive IFN.

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is an acceptable regimen for treatment-experienced (nonresponder) HIV/HCV-coinfected patients with HCV genotype 1 infection.**

  Rating: Class IIb, Level C

Alternative regimen(s) for treatment-naive and PEG/RBV relapser, HIV/HCV-coinfected patients with genotype 2 or 3 infection.

- **None**

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponder) HIV/HCV-coinfected patients with genotype 2 or 3 infection who are eligible to receive IFN.

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is an acceptable regimen for treatment-experienced IFN-eligible persons with HCV genotype 2 or 3 infection.**

  Rating: Class IIa, Level C

Alternative regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with HCV genotype 4, 5, or 6 infection.

- **None**

The TMC435-C212 is a Phase III, open-label, single-arm study investigating simeprevir plus PEG/RBV (fixed-dose ribavirin) in treatment-naive and treatment-experienced patients coinfected with HCV genotype-1 and HIV. (Dieterich, 2013) The study used an RGT design for treatment-naive and prior PEG/RBV relapsers; prior partial and null responders and all patients with cirrhosis (regardless of treatment history) received 48 weeks of therapy (SMV x 12 weeks plus PEG/RBV x 48 weeks). The primary analysis reported an overall SVR12 of 74% (treatment naive: 79%; prior relapsers, 87%: prior partial responders: 70%; prior null responders: 57%). Most (89%) eligible patients met criteria for RGT and were able to shorten therapy to 24 weeks, after which time 78% achieved SVR12. Lower SVR12 was reported in several clinically relevant subgroups: genotype 1a (71% vs 89% in genotype 1b); genotype 1a with the Q80K mutation at baseline (67%); advanced fibrosis or cirrhosis (64%); IL28B unfavorable genetic polymorphisms (68% and 61% for the CT and TT variants vs 96% for the favorable CC variant); high baseline HCV RNA (70% for >800,000 IU/mL or 93% for <800,000 IU/mL); and patients not receiving antiretroviral therapy (62% vs 75% in subjects on antiretroviral drugs). As with patients with HCV monoinfection, baseline resistance testing for the Q80K polymorphism should be performed in all patients harboring the genotype 1a subtype and a different regimen considered if the polymorphism is present. Virologic failures occurred; most failures (79%) were associated with the emergence of resistant-associated mutations.

The adverse event profile was similar to that of patients with HCV monoinfection, with a higher frequency of pruritus, rash, photosensitivity, and increased bilirubin than is observed in patients receiving PEG/RBV alone. Due to the complexity of antiretroviral drug-associated drug interactions with simeprevir, the longer course of PEG/RBV, the adverse effect profile, and the risk of resistance emergence with treatment failure, simeprevir plus PEG/RBV is considered an alternative regimen for treatment-naive and prior PEG/RBV relapse patients with HIV coinfection with genotype HCV who cannot tolerate the recommended regimens. This regimen is not recommended in prior nonresponders or patients with cirrhosis because of observed lower response rates seen and the poor tolerability of 48 weeks of PEG/RBV. Due to diminished activity in vitro (for genotype 2 and 3) and insufficient data (for genotype 4) this regimen cannot be recommended for these genotypes.

Sofosbuvir plus PEG/RBV has not been studied in patients with HIV/HCV genotype 1 coinfection in whom previous IFN-based HCV therapy has failed. However, in a study of a limited number of patients (n=19), the efficacy of this regimen in treatment-naive subjects with HIV/HCV genotype 1 coinfection was equivalent to that in patients with HCV monoinfection. (Rodriguez-Torres, 2013) An exploratory FDA analysis estimated the SVR rate of this regimen to be 78% among a treatment-experienced population with HCV monoinfection, including 71% in those with multiple poor pretreatment response predictors. (US FDA, 2013b) These data, along with the absence of antiretroviral drug limitations, support inclusion of this regimen as a recommended option for treatment-experienced patients with HIV/HCV coinfection.

Sofosbuvir plus RBV has not been studied in prior HCV treatment-experienced patients with HIV/HCV genotype 1 coinfection. This regimen yielded an SVR12 rate of 76% among treatment-naive HIV/HCV genotype 1-coinfected patients. (Sulkowski, 2013b) However, responses to this regimen are expected to be lower in treatment-experienced coinfected subjects based on limited data in treatment-experienced HCV-monoinfected patients treated for 12 weeks with sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily in divided doses). (Gane, 2013a) Further, response rates are expected to be lower than those associated with the recommended and alternative regimens. This regimen should be reserved for coinfected patients who cannot tolerate IFN and do not have antiretroviral regimen options compatible with simeprevir. These patients require expert consultation with careful consideration of fibrosis stage; in some cases, deferral of therapy may be a more appropriate action.

Sofosbuvir plus PEG/RBV has not been studied in patients with HIV/HCV genotype 2 or 3 coinfection in whom previous IFN-based HCV therapy has failed. However, recognizing the potential limitations of sofosbuvir plus RBV in more difficult to treat genotype 2 and 3 patients, particularly those with prior nonresponse and cirrhosis, the addition of IFN to the regimen can be considered for those patients who are eligible. The LONESTAR-2 (open-label, single-site, single-arm phase 2 trial) evaluated PEG (180 µg weekly), sofosbuvir (400 mg once daily), and weight-based RBV (1000 mg to 1200 mg daily in divided doses) for 12 weeks in HCV-monoinfected treatment-experienced patients with genotype 2 or 3 infection. Cirrhosis was present at baseline in 55% of patients. Overall, SVR12 was achieved in 96% (22 of 23) of those with genotype 2 infection. SVR occurred in 93% (13/14) and 100% (9 of 9) of patients with and without cirrhosis, respectively. Because sofosbuvir is safe and effective when used to treat HIV/HCV-coinfected patients, the combination of sofosbuvir plus PEG/RBV for 12 weeks can be considered for appropriate genotype 2 and 3 HIV/HCV-coinfected patients.

The following regimens are NOT recommended for treatment-naive or treatment-experienced HIV/HCV-coinfected patients

- **PEG/RBV with or without telaprevir or boceprevir for 24 to 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

Due to its prolonged treatment course, adverse effects, and poor response rates, PEG/RBV is no longer recommended for the treatment of patients with HCV genotypes 1, 2, 3, or 4 who are coinfected with HIV. Neither telaprevir nor boceprevir is approved for use in patients with HIV/HCV coinfection. However, when combined with PEG/RBV and used for 48 weeks, these drugs have reported efficacy and safety in patients with HIV/HCV genotype 1 coinfection similar to that in patients with HCV genotype 1 monoinfection. (Sulkowski, 2013d); (Sulkowski, 2013a) Ongoing Phase III trials will investigate the use of RGT for select patient groups. Telaprevir and boceprevir are each substrates and inhibitors of CYP3A4 and thus have substantial drug interactions with antiretroviral drugs. (van Heeswijk, 2011a); (van Heeswijk, 2011b); (Kakuda, 2012); (Johnson, 2013); (Kasserra, 2011); (Hulskotte, 2013); (Garraffo, 2013); (de Kanter, 2012); (Hammond, 2013); (Vourvahis, 2013) Due to the adverse effect profile, prolonged required course of PEG/RBV, and substantial drug interactions, these agents are no longer recommended for HIV/HCV-coinfected patients.

Because of their limited activity in vitro and in vivo against HCV genotypes 2 and 3, boceprevir, telaprevir, and simeprevir should not be used as therapy for HIV/HCV-coinfected patients with HCV genotype 2 or 3 infection. Boceprevir and telaprevir also have limited activity against HCV genotype 4 and should not be used as therapy for HIV/HCV coinfected patients with HCV genotype 4 infection. There are currently not enough data to support a recommendation for the use of simeprevir for genotype 4 infection in HIV/HCV-coinfected patients.

2. Patients with Cirrhosis

The summary of recommendations for patients with cirrhosis is in the box.

Compensated Cirrhosis

Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.

Rating: Class I, Level A

This statement is supported by a number of studies (described above) that included patients with compensated cirrhosis who were evaluated in sub-group analyses.

Decompensated Cirrhosis

Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).

Rating: Class I, Level C

If the decision to treat has been made, the recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. This regimen should be used only by highly experienced HCV providers

Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks

Rating: Class IIb, Level B

In one study, 61 patients with HCV infection and hepatocellular carcinoma meeting MILAN criteria for liver transplant were treated with sofosbuvir plus RBV for up to 48 weeks. (Curry MP, 2013) At the time of treatment initiation, the median MELD score was 8 (range: 6-14), and 17 patients had CTP scores of 7 or 8 (CTP Class B). To date, 44 patients have undergone liver transplantation, of whom 41 (93%) had HCV RNA below the lower limit of quantification. At 12 weeks post-transplant, 23 of 37 (62%) had no detected HCV RNA consistent with prevention of recurrent HCV infection. In the post-transplant period, 10 patients experienced recurrent HCV infection. Among the 10 patients who experienced recurrent graft infection, 9 had HCV RNA not detected for less than 30 days pretransplant. The most common adverse effects were fatigue, anemia, and headache; adverse effects led to treatment discontinuation for 2 patients (3%).

In a sofosbuvir compassionate-use program for patients with severe recurrent HCV infection following liver transplantation who were predicted to have a less than 6-month survival, (Forns, 2013b) 44 patients were treated with sofosbuvir plus RBV 32 patients were also given PEG. At treatment initiation, the median MELD score was 16 (range: 6-43), and fibrosing cholestatic hepatitis was documented in 20 patients. After week 12 of treatment, 91% of patients treated with sofosbuvir plus RBV and 75% of those treated with the addition of PEG achieved HCV RNA less than the lower limit of quantification. Of 27 patients evaluated at 12 weeks post-treatment, 15 patients (56%) achieved SVR. Overall, 75% had improved or stable clinical liver disease including improvement in hyperbilirubinemia and coagulopathy as well as decrease in MELD score. In this very sick population, 8 patients died, most from liver disease progression.

The following regimens are NOT recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C):

- **Any IFN-based therapy**

  Rating: Class III, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir-, boceprevir-, or simeprevir-based regimens**

  Rating: Class III, Level A

IFN should not be given to patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) because of the potential for worsening hepatic decompensation. Neither telaprevir nor boceprevir should be used for this population because they must be coadministered with PEG/RBV. Very minimal data exist for the use of simeprevir in patients with decompensated cirrhosis. Until additional data become available, simeprevir should not be used in patients with decompensated cirrhosis.

3. Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation

The summary of recommendations for patients who develop recurrent HCV infection post-liver transplantation is in the box.

Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg), for 12 weeks to 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level for 24 weeks is recommended for patients with compensated allograft HCV genotype 2 or 3 infection.

Rating: Class IIb, Level C

Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis.

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level, with or without PEG (in the absence of contraindication to its use), for 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Simeprevir has not been studied with sofosbuvir in the post-transplant setting; however, drug interaction studies in non-infected participants indicate that simeprevir can be dosed safely in conjunction with calcineurin inhibitors. Based on these data, clinicians may consider the use of sofosbuvir plus simeprevir as described for non-transplant patients, particularly in those expected to have difficulty tolerating RBV (eg, patients with impaired renal function and anemia). Consideration should be given to pretreatment resistance testing for the Q80K polymorphism in genotype 1a-infected patients.

In addition to the sofosbuvir compassionate-use program, (Forns, 2013a) 40 patients with recurrent HCV infection following liver transplantation were treated for 24 weeks with sofosbuvir (400 mg daily) plus RBV (starting at 600 mg daily followed by dose escalation as tolerated). (Charlton, 2013) At study entry, patients were required to be at least 6 months post-transplant, to have a CTP score of 7 or lower, and to have a MELD score of 17 or lower. Bridging fibrosis or cirrhosis was documented in 25 patients (63%). At the end of treatment, all patients had HCV RNA levels below the lower limit of quantification and, at 4 weeks after treatment discontinuation, 27 of 35 patients (77%) had undetectable levels of HCV RNA. The most common adverse events were fatigue, headache, and arthralgia. Anemia was reported in 20% of patients. Two patients discontinued therapy due to adverse events. No deaths, graft loss, or episodes of rejection were reported.

The addition of PEG to sofosbuvir plus RBV may also be considered in the absence of contraindications.

The following regimens are NOT recommended for treatment-naive patients with compensated allograft hepatitis C virus infection.

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir- based regimens should not be used for patients with compensated allograft hepatitis C virus infection.**

  Rating: Class III, Level A

Telaprevir or boceprevir should not be used in the post-liver transplant population because of surrounding toxicity and drug interactions with calcineurin inhibitors.

Decompensated Cirrhosis

Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Rating: Class I, Level C

4. Patients with Renal Impairment, Including Severe Renal Impairment (CrCl <30 mL/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis

Summary of Recommendations for Patients with Renal Impairment Including, Severe Renal Impairment (CrCl <30 mL/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis is found in the Unique Patient Populations: Renal Impairment Box.

When using sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes, no dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ≥30 mL/min). Sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require hemodialysis, because no dosing data are currently available for this patient population.

Rating: Class IIa, level B

Sofosbuvir enters the hepatocyte, where it is metabolized to its active form, GS-461203. The downstream inactive nucleoside metabolite GS-331007 is almost exclusively eliminated from the body renally, mediated through a combination of glomerular filtration and active tubular secretion. Results of phase 2 and 3 sofosbuvir clinical trials have excluded patients with serum Cr level above 2.5 and/or CrCl level below <60 mL/min. The pharmacokinetics of a single dose of sofosbuvir 400 mg was assessed in persons not infected with HCV (study P7977-0915) with mild (estimated glomerular filtration rate [eGFR] ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR <30 mL/min/1.73m^2) and persons with ESRD requiring hemodialysis. Relative to persons with normal renal function (eGFR >80 mL/min/1.73m^2), the sofosbuvir AUC (0-inf) was 61%, 107%, and 171% higher in subjects with mild, moderate, and severe renal impairment, respectively. The GS-331007 AUC (0-inf) was 55%, 88%, and 451% higher, respectively. No safety signals have been seen under similar conditions. In subjects with ESRD (relative to subjects with normal renal function), sofosbuvir and GS-331007 AUC (0-inf) was 28% and 1280% higher, respectively, when sofosbuvir was dosed 1 hour before hemodialysis, compared with 60% and 2070% higher, respectively, when sofosbuvir was dosed 1 hour after hemodialysis. No dose adjustment is required for patients with mild or moderate renal impairment. The safety of sofosbuvir has not been established in patients with severe renal impairment or ESRD. Therefore, a dose recommendation cannot be provided for these populations at this time, although a dedicated study to evaluate optimal dosing of sofosbuvir in HCV-infected patients with severe renal impairment or ESRD on hemodialysis is currently underway.

When using simeprevir in treatment/retreatment of HCV-infected patients, no dosage adjustment is required for patients with mild to moderate to severe renal impairment. Simeprevir has not been studied in patients with ESRD, including those requiring hemodialysis.

Rating: Class IIa, level B

Simeprevir is primarily metabolized by liver CYP3A4, and renal clearance plays an insignificant role (<1%) in the elimination of simeprevir and its metabolites.

Simeprevir 150 mg daily for 7 days has been studied in non-HCV infected patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) and healthy volunteers (eGFR > mL/min/1.73 m^2). For persons with severe renal impairment, simeprevir C_{min}, C_{max}, and AUC (24 hour) were 71%, 34%, and 62% higher, respectively, compared with matched healthy controls. Simeprevir exposure was higher in patients with severe renal impairment (steady-state by day 7), but no significant difference was observed in simeprevir plasma protein binding. Simeprevir was generally safe and well tolerated in subjects with severe renal impairment. Therefore, no dose adjustment of simeprevir is required in these patients. No clinically significant differences in pharmacokinetics were observed in HCV-uninfected participants with mild, moderate, or severe renal impairment. CrCl level was not identified as a significant covariate of simeprevir population pharmacokinetics in HCV-infected patients. Simeprevir has not been evaluated in patients receiving hemodialysis.

In patients with renal impairment/ESRD/HD, dosing of PEG and RBV should follow updated FDA recommendations or package insert recommendations based on calculated GFR. Caution should be used in administering RBV to these patients, and close monitoring of hemoglobin is required.

Rating: Class IIa, level B

HCV infection is a major health problem in patients with ESRD. The incidence of acute HCV infection during maintenance dialysis is much higher than that in the general population because of the risk for nosocomial transmission. The kidney is important for the catabolism and filtration of both IFN and RBV, and therefore, reduced doses of both PEG and RBV are warranted in patients with ESRD.

Impaired excretion of RBV occurs in patients with chronic kidney disease, as RBV is mostly eliminated by the kidney. Very little RBV is removed via dialysis. Thus, the drug can accumulate, exacerbating hemolysis in the dialysis population already at substantial risk for anemia. If a decision is made to use RBV in patients on maintenance hemodialysis, it should be used only after the implementation of several safety precautions, including (1) administering very low doses of RBV (200 mg daily), (2) monitoring hemoglobin levels on a weekly basis, (3) titrating epoetin alfa to treat anemia, and (4) providing intravenous iron supplementation to boost erythropoietin activity.

Dose adjustments needed for patients with renal impairment are summarized in the Renal Impairment Table.

Unique Patient Populations: HIV/HCV Coinfection Box. Recommendations for HIV/HCV Coinfected Patients Who are Being Treated for HCV, by Genotype

Genotype	Recommended	Alternative	NOT Recommended	Allowable Antiretroviral Therapy
1	**Treatment-naive and prior PEG/RBV relapsers** **IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + RBV x 24 weeks SOF + SMV ± RBV x 12 weeks **Treatment experienced (prior PEG/RBV nonresponders) regardless of IFN eligibility:** SOF + SMV ± RBV x 12 weeks	**Treatment-naive and prior PEG/RBV relapsers** **IFN eligible:** SMV x 12 weeks + PEG/RBV x 24 weeks* **IFN ineligible:** None **Treatment experienced (prior PEG/RBV nonresponders)** **IFN eligible:** SOF + PEG/RBV x 12 Weeks **IFN ineligible:** SOF + RBV x 24 Weeks	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks SMV x 12 weeks + PEG/RBV x 48 wks	**For SOF use:** ALL except didanosine, zidovudine **For SMV use:** LIMITED to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir
2	SOF + RBV x 12 weeks regardless of treatment history	**Treatment naive and prior PEG/RBV relapsers: None** **Treatment experienced (prior PEG/RBV nonresponders)** **IFN eligible:** SOF + PEG/RBV X 12 Weeks **IFN ineligible:** None	PEG/RBV x 24-48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine
3	SOF + RBV x 24 weeks regardless of treatment history	**Treatment naive and PEG/RBV relapsers: None** **Treatment experienced (prior PEG/RBV nonresponders)** **IFN eligible:** SOF + PEG/RBV X 12 Weeks **IFN ineligible:** None	PEG/RBV x 24 - 48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine
4	**Regardless of treatment history:** **IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + RBV x 24 weeks	None	PEG/RBV x 48 weeks Any regimen with TVR or BOC	ALL except didanosine, zidovudine
5 or 6	**Regardless of treatment history:** SOF + PEG/RBV x 12 weeks	None	PEG/RBV x 48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine

*For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if present

Unique Patient Populations: Cirrhosis Box. Summary of Recommendations for Patients with Cirrhosis

Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.

Rating: Class I, Level A

Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).

Rating: Class I, Level C

The recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. This regimen should be used only by highly experienced HCV providers

Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks

Rating: Class IIb, Level B

The following regimens are NOT recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C):

- **Any IFN-based therapy**

  Rating: Class III, Level A
- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A
- **Telaprevir-, boceprevir-, or simeprevir-based regimens**

  Rating: Class III, Level A

Unique Patient Population: Post-Liver Transplantation Box. The summary of recommendations for patients who develop recurrent HCV infection post-liver transplantation

Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg), for 12 weeks to 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level for 24 weeks is recommended for patients with compensated allograft HCV genotype 2 or 3 infection.

Rating: Class IIb, Level C

Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis.

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level, with or without PEG (in the absence of contraindication to its use), for 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

The following regimens are NOT recommended for treatment-naive patients with compensated allograft hepatitis C infection

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir- based regimens should not be used for patients with compensated allograft hepatitis C infection.**

  Rating: Class III, Level A

Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Rating: Class I, Level C

Renal Impairment Box. Summary of recommendations for Patients with Renal Impairment, Including Severe Renal Impairment (CrCl <30 ML/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis

When using sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes, no dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ≥30 mL/min). Sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require hemodialysis, because no dosing data are currently available for this patient population.

Rating: Class IIa, level B

When using simeprevir in treatment/retreatment of HCV-infected patients, no dosage adjustment is required for patients with mild to moderate to severe renal impairment. Simeprevir has not been studied in patients with ESRD, including those requiring hemodialysis.

Rating: Class IIa, level B

In patients with renal impairment/ESRD/HD, dosing of PEG and RBV should follow updated FDA recommendations or package insert recommendations based on calculated GFR. Caution should be used in administering RBV to these patients, and close monitoring of hemoglobin is required.

Rating: Class IIa, level B

Unique Patient Populations: Renal Impairment Table. Dose Adjustments Needed for Patients with Renal Impairment

Renal Impairment	eGFR/CrCl level (mL/min/ 1.73 m^2)	Interferon	Ribavirin	Sofosbuvir	Simeprevir
Mild	50-80	180 µg PEG (2a); PEG (2b) 1.5 µg/kg	Standard	Standard	Standard
Moderate	30-50	180 µg PEG (2a); PEG alfa-2b1 µg/kg or 25% reduction	Alternating doses 200 and 400 mg every other day	Standard	Standard
Severe	<30	135 µg PEG (2a); PEG (2b)1 µg/kg or 50% reduction	200 mg/d	Data not available	Standard
ESRD/HD		PEG (2a) 135 µg/wk or PEG (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Data not available	Data not available

REFERENCES

Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;

Alter MJ, Kuhnert WL, Finelli L. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2003;52(RR-3):1-13, 15.

Alvarez D, Dieterich DT, Brau N, Moores L, Ball L, Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. *J Viral Hepat*. 2006;13:683-689.

American Heart Association. http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf. Accessed on January 27, 2014.

Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006;144(10):705-714.

Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med*. 2011;364(23):2199-2207.

Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1207-1217.

Bellentani S, Pozzato G, Saccoccio G, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. *Gut*. 1999;44(6):874-880.

Berenguer J, Álvarez-Pellicer J, Martin PM, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. *Hepatology*. 2009;50(2):407-413.

Bravo MJ, Vallejo F, Barrio G, et al. HCV seroconversion among never-injecting heroin users at baseline: no predictors identified other than starting injection. *Int J Drug Policy*. 2012;23(5):415-419.

Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. *Clin Infect Dis*. 2013;57 Suppl 2:S56-S61.

Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. *Gastroenterology*. 2012;142(6):1293-1302.

Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Morb Mortal Wkly Rep*. 1998;47(RR-19):1-39.

Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57(RR-8)

Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. *MMWR Morb Mortal Wkly Rep*. 2013;62(18):362-365.

Charlton MR, Gane E, Manns M, et al. Sofosbuvir and Ribavirin for the Treatment of Established Recurrent Hepatitis C Infection After Liver Transplantation: Preliminary Results of a Prospective, Multicenter Study. *Hepatology: Special Issue: The 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013*. 2013;Vol 58(4):1378A.

Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med*. 2013;158(11):807-820.

Clark BT, Garcia-Tsao G, Fraenkel L. Patterns and predictors of treatment initiation and completion in patients with chronic hepatitis C virus infection. *Patient Prefer Adherence*. 2012;6:285-295.

Coilly A, Roche B, Dumortier J, et al. Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: A multicenter experience. *J.Hepatol*. 2014;60(1):78-86.

Corrao G, Arico S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *Hepatology*. 1998;27(4):914-919.

Crippin JS, McCashland T, Terrault N, Sheiner P, Charlton MR. A pilot study of the tolerability and efficacy of antiviral therapy in hepatitis C virus-infected patients awaiting liver transplantation. *Liver Transpl*. 2002;8(4):350-355.

Curry MP, et al. Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection after Liver Transplantation. 64th Annual Meeting of the American Association for the Study of Liver Disease. Nov 1-5, 2013, 2013; Washington, DC.

de Kanter C, Blonk M, Colbers A et al. The influence of the HCV protease inhibitor boceprevir on the pharmacokinetics of the HIV integrase inhibitor raltegravir [Abstract 772LB]. 19th Conference on Retroviruses and Opportunistic Infections (CROI). March 5-8, 2012; Seattle, WA.

de Ledinghen V, Barreiro P, Foucher J, et al. Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. *J Viral Hepat*. 2008;15(6):427-433.

Di Bisceglie A, Kuo A, Rustgi V, Sulkowski M. Virological Outcomes and Adherence to Treatment Algorithms in a Longitudinal Study of Patients with Chronic Hepatitis C Treated with Boceprevir or Telaprevir in the U.S. (HCV-TARGET). AASLD The Liver Meeting. Nov 1-5, 2013, 2013; Washington, DC; 2013.

Dieperink E, Ho SB, Heit S, Durfee JM, Thuras P, Willenbring ML. Significant reductions in drinking following brief alcohol treatment provided in a hepatitis C clinic. *Psychosomatics*. 2010;51(2):149-156.

Dieterich D, Rockstroh J, Orkin C, et al. Simeprevir (TMC435) plus peginterferon/ribavirin in patients co-infected with HCV genotype-1 andHIV-1: primary analysis of the C212 study. 14th European AIDs Conference (EACS 2013). Oct 16-19, 2013, 2013; Brussels.

Fierer DS, Dieterich DT, Fiel MI, et al. Rapid progression to decompensated cirrhosis, liver transplant, and death in HIV-infected men after primary hepatitis C virus infection. *Clin Infect Dis*. 2013;56(7):1038-1043.

Fierer DS, Uriel AJ, Carriero DC, et al. Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study. *J Infect Dis*. 2008;198(5):683-686.

Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. *Clin Infect Dis*. 2004;38:e79-e80.

Fontana RJ, Sanyal AJ, Ghany MG, et al. Factors that determine the development and progression of gastroesophageal varices in patients with chronic hepatitis C. *Gastroenterology*. 2010;138(7):2321-31, 2331.

Forns X, Fontana RJ, Moonka D, et al. Initial Evaluation of the Sofosbuvir Compassionate Use Program for Patients with Severe Recurrent HCV Following Liver Transplantation. Special Issue: The 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013. Epub Oct 1, 2013, 10-1-2013a;732A.

Forns X, Lawitz E, Zeuzem S, et al. Simeprevir (TMC435) with peg-interferon a-2a/ribavirin for treatment of chronic HCV genotype 1 infection in patients who relapsed after previous interferon-based therapy: efficacy and safety in patient sub-populations in the PROMISE phase III trial. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Nov 1-5, 2013, 2013b; Washington, DC.

Foster GR, Hezode C, Bronowicki JP, et al. Telaprevir alone or with peginterferon and ribavirin reduces HCV RNA in patients with chronic genotype 2 but not genotype 3 infections. *Gastroenterology*. 2011;141(3):881-889.

Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013a;368(1):34-44.

Gane EJ, Stedman CA, Hyland RH, et al. Once daily sofosbuvir plus ribavirin for 12 and 24 weeks in treatment-naive patients with HCV infection: the QUANTUM study. Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver. April 24-28, 2013, 2013b; Amsterdam, the Netherlands.

Garraffo R, Poizot-Martin I, Piroth L et al. Pharmacokinetic (PK) interactions between Boceprevir (BOC) and Atazanavir/r (ATV/r) or Raltegravir (RAL) in HIV/HCV coinfected patients (pts). 14th International Workshop on Clinical Pharmacology on HIV Therapy. April 22-24, 2013; Amsterdam, the Netherlands.

Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(4):1433-1444.

Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49(4):1335-1374.

Gilead Sciences I. Sofosbuvir [package insert]. 2013. Foster City, CA, Gilead Sciences, Inc.

Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review. *AIDS*. 2012;26(16):2059-2067.

Hammond KP, Wolfe P, Burton JR, Jr., et al. Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers. *J Acquir Immune Defic Syndr*. 2013;62(1):67-73.

Harris DR, Gonin R, Alter HJ, et al. The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presence of alcohol abuse. *Ann Intern Med*. 2001;134(2):120-124.

Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. *N Engl J Med*. 2013;368(20):1859-1861.

Hosein SR, Wilson DP. HIV, HCV, and drug use in men who have sex with men. *Lancet*. 2013;382(9898):1095-1096.

Hourigan LF, Macdonald GA, Purdie D, et al. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology*. 1999;29(4):1215-1219.

Hulskotte EG, Feng HP, Xuan F, et al. Pharmacokinetic interactions between the hepatitis C virus protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, darunavir, and lopinavir. *Clin Infect Dis*. 2013;56(5):718-726.

Islam MM, Topp L, Conigrave KM, et al. Linkage into specialist hepatitis C treatment services of injecting drug users attending a needle syringe program-based primary healthcare centre. *J Subst Abuse Treat*. 2012;43(4):440-445.

Jacobson IM, Dore GJ, Foster G, et al. Simeprevir (TMC435) with Peginterferon/ Ribavirin for Chronic HCV Genotype-1 Infection in Treatment-Naive Patients: Results From QUEST-1, a Phase III Trial. Digestive Disease Week. May 18-21, 2013; Orlando, FL.

Jacobson IM, Ghalib RH, Rodriguez-Torres M, et. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. *Hepatology: Special Issue: The 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013*. 2013;58(4):1379A.

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368(20):1867-1877.

Janssen Therapeutics. Simeprevir [package insert]. 2013. Titusville, NJ, Janssen Therapeutics.

Johnson M, Borland J, Chen S-J et al. Dolutegravir, Boceprevir, Telaprevir PK: The effect of Boceprevir and Telaprevir on Dolutegravir Pharmacokinetics, in Healthy Adult Subjects. 14th International Workshop on Clinical Phamacology of HIV Therapy. Apr 22-24, 2013, 2013; Amsterdam.

Kakuda T, Leopold L, Nijs S. Pharmacokinetic interaction between etravirine or rilpivirine and telaprevir in healthy volunteers: a randomised, two-way crossover trial [Abstract O-18]. 13th International Workshop on Clinical Pharmacology of HIV Therapy. April 16-18, 2012; Barcelona, Spain.

Kasserra C, Hughes E, Treitel M, Gupta S, O'Mara E. Clinical Pharmacology of BOC: Metabolism, Excretion, and Drug-Drug Interactions. In: Proceedings from the 18th Conference on Retroviruses and Opportunistic Infections (CROI): February 27-March 2. 2011; Boston, MA. Abstract 118.

KDIGO. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl*. 2008;(109):S1-99.

Khokhar OS, Lewis JH. Reasons why patients infected with chronic hepatitis C virus choose to defer treatment: do they alter their decision with time? *Dig Dis Sci*. 2007;52(5):1168-1176.

Kirby B, Mathias A, Rossi S, et al. No clinically significant pharmacokinetic drug interactions between sofosbuvir (GS-7977) and HIV antiretrovirals atripla, rilpivirine, darunavir/ritonavir, or raltegravir in healthy volunteers. 63rd Annual Meeting of the American Association of the Study of Liver Diseases (AASLD) 2012. Nov 9-11, 2012, 2013; Boston, MA.

Kleiner DE. The liver biopsy in chronic hepatitis C: a view from the other side of the microscope. *Semin Liver Dis*. 2005;25(1):52-64.

Lai JC, Kahn JG, Tavakol M, Peters MG, Roberts JP. Reducing infection transmission in solid organ transplantation through donor nucleic Acid testing: a cost-effectiveness analysis. *Am J Transplant*. 2013;13(10):2611-2618.

Lalezari L, Nelson DR, Hyland RH, et al. Once daily sofosbuvir plus ribavirin for 12 and 24 weeks in treatment-naive patients with HCV infection: the QUANTUM study. Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver. April 24-28, 2013, 2013; Amsterdam, The Netherlands.

Larney S, Kopinski H, Beckwith CG, et al. Incidence and prevalence of hepatitis C in prisons and other closed settings: Results of a systematic review and meta-analysis. *Hepatology*. 2013;58(4):1215-1224.

Lawitz E, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013a;369(7):678-679.

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013b;368(20):1878-1887.

Lee SR, Kardos KW, Schiff E, et al. Evaluation of a new, rapid test for detecting HCV infection, suitable for use with blood or oral fluid. *J Virol Methods*. 2011;172(1-2):27-31.

Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology. 2007;46(5):1453-1463.

Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. *JAMA*. 2012;308(4):370-378.

Linas BP, Wong AY, Schackman BR, Kim AY, Freedberg KA. Cost-effective screening for acute hepatitis C virus infection in HIV-infected men who have sex with men. *Clin Infect Dis*. 2012;55(2):279-290.

Mahajan R, Liu SJ, Klevens RM, Holmberg SD. Indications for testing among reported cases of HCV infection from enhanced hepatitis surveillance sites in the United States, 2004-2010. *Am J Public Health*. 2013;103(8):1445-1449.

McGowan CE, Monis A, Bacon BR, et al. A global view of hepatitis C: physician knowledge, opinions, and perceived barriers to care. *Hepatology*. 2013;57(4):1325-1332.

Mehta SH, Lucas GM, Mirel LB, et al. Limited effectiveness of antiviral treatment for hepatitis C in an urban HIV clinic. *AIDS*. 2006;20(18):2361-2369.

Miller L, Fluker SA, Osborn M, Liu X, Strawder A. Improving access to hepatitis C care for urban, underserved patients using a primary care-based hepatitis C clinic. *J Natl Med Assoc*. 2012;104(5-6):244-250.

Mira JA, Rivero-Juárez A, López-Cortes LF, et al. Benefits from sustained virologic response to pegylated interferon plus ribavirin in HIV/hepatitis C virus-coinfected patients with compensated cirrhosis. *Clin Infect Dis*. 2013;56(11):1646-1653.

Moreno C, Herzode C, Marcellin P, et al. Simeprevir with peginterferon/ribavirin in treatment-naïve or experienced patients with chronic HCV genotype 4 infection: Interim results of a Phase III trial. 14th European AIDS conference Brussels Belgium Oct 2013. Oct 16-19, 2013, 2013; Brussels, Belgium.

Morrill JA, Shrestha M, Grant RW. Barriers to the treatment of hepatitis C. Patient, provider, and system factors. *J Gen Intern Med*. 2005;20(8):754-758.

Moyer VA. Screening for HIV: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2013;159(1):51-60.

Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology*. 2010;52(1):79-104.

Noda K, Yoshihara H, Suzuki K, et al. Progression of type C chronic hepatitis to liver cirrhosis and hepatocellular carcinoma--its relationship to alcohol drinking and the age of transfusion. *Alcohol Clin Exp Res*. 1996;20(1 Suppl):95A-100A.

Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. *Am J Gastroenterol*. 2002;97(9):2408-2414.

Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *JAMA*. 2013;310(8):804-811.

Ouwerkerk-Mahadevan S, Sekar V, Peeters M, Beumont-Mauviel M. The pharmokinetic interactions of HCV protease inhibitor TMC435 with RPV, TDF, EFV, or RAL in health volunteers [Abstract 49]. 19th Conference on Retroviruses and Opportunistic Infections (CROI). March 5-8, 2012; Seattle, Washington.

Pawlotsky JM. Use and interpretation of virological tests for hepatitis C. *Hepatology*. 2002;36(5 Suppl 1):S65-S73.

Poordad F, Manns MP, Marcellin P, et al. Simeprevir (TMC435) with Peginterferon/Ribavirin for Treatment of Chronic HCV Genotype-1 Infection in Treatment-Naive Patients: Results From QUEST-2, a Phase III Trial. Digestive Disease Week. May 18-21, 2013, 2013; Orlando, FL.

Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. 1997;349(9055):825-832.

Proeschold-Bell RJ, Patkar AA, Naggie S, et al. An integrated alcohol abuse and medical treatment model for patients with hepatitis C. *Dig Dis Sci*. 2012;57(4):1083-1091.

Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002;97(10):2614-2618.

Reilley B, Leston J, Redd JT, Geiger R. Lack of Access to Treatment as a Barrier to HCV Screening: A Facility-Based Assessment in the Indian Health Service. *J Public Health Manag Pract*. 2013.

Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. *Hepatology*. 2006;43(2 Suppl 1):S113-S120.

Rodriguez-Torres M, Rodriguez-Orengo JF, Gaggar A, et al. Sofosbuvir and Peginterferon Alfa-2a/Ribavirin for Treatment-Naïve Genotype 1?4 HCV-Infected Patients Who Are Coinfected With HIV. 53rd ICAAC 2013. Sept 10-13, 2013, 2013; Denver, CO.

Rossaro L, Torruellas C, Dhaliwal S, et al. Clinical Outcomes of Hepatitis C Treated with Pegylated Interferon and Ribavirin via Telemedicine Consultation in Northern California. *Dig Dis Sci*. 2013;58(12):3620-3625.

Ruane P, Ain D, Meshrekey R, Stryker R. Sofosbuvir Plus Ribavirin in the Treatment of Chronic HCV Genotype 4 Infection in Patients of Egyptian . Ancestry AASLD The Liver Meeting 2013. Nov 2, 2013, 2013; Washington DC.

Safdar K, Schiff ER. Alcohol and hepatitis C. *Semin Liver Dis*. 2004;24(3):305-315.

Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. *Hepatology*. 2006;43(6):1303-1310.

Schmidt AJ, Falcato L, Zahno B, et al. Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection? *BMC Public Health*. 2014;14(1):3.

Seem DL, Lee I, Umscheid CA, Kuehnert MJ. Excerpt from PHS guideline for reducing HIV, HBV and HCV transmission through organ transplantation. *Am J Transplant*. 2013;13(8):1953-1962.

Shaw K, Gennat H, O'Rourke P, Del MC. Exercise for overweight or obesity. *Cochrane Database Syst Rev*. 2006;(4):CD003817.

Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med*. 2003;139(6):493-498.

Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep*. 2012;61(RR-4):1-32.

Stein MR, Soloway IJ, Jefferson KS, Roose RJ, Arnsten JH, Litwin AH. Concurrent group treatment for hepatitis C: implementation and outcomes in a methadone maintenance treatment program. *J Subst Abuse Treat*. 2012;43(4):424-432.

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013.

Sulkowski M, Pol S, Mallolas J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. *Lancet Infect Dis*. 2013a;13(7):597-605.

Sulkowski M, Rodriguez-Torres M, Lalezari J, et al. All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV (PHOTON-1) . *Hepatology*. 2013b;58(Number 4 Suppl 1):313A.

Sulkowski M, Rodriguez-Torres M, Lalezari JP, et al. All-Oral Therapy with Sofosbuvir Plus Ribavirin for the treatment of HCV genotype 1,2 and 3 infection in patients coinfected with HIV (PHOTON-1). AASLD Annual Meeting 2013. Nov 1-5, 2013, 2013c; Washington, DC.

Sulkowski MS, Sherman KE, Dieterich DT, et al. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. *Ann Intern Med*. 2013d;159(2):86-96.

Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS*. 2008;22(15):1979-1991.

Thomas DL. The challenge of hepatitis C in the HIV-infected person. *Annu Rev Med*. 2008;59:473-485.

Urbanus AT, van de Laar TJ, Stolte IG, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. *AIDS*. 2009;23(12):F1-F7.

US FDA. FDA Antiviral Drugs Advisory Committee Meeting October 25, 2013: Background Package for NDA 204671 Sofosbuvir (GS-7977).http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm371875.htm. Accessed on November 15, 2013.

US FDA. FDA Introductory Remarks: Sofosbuvir NDA 204671. Presented on October 25, 2013.http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM375285.pdf. Accessed on December 6, 2013.

US Preventive Services Task Force. Screening for hepatitis C virus infection in adults: US Preventive Services Task Force recommendation statement. http://www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm. Accessed on October 28, 2013.

van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. *Gastroenterology*. 2009;136(5):1609-1617.

van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. *AIDS*. 2010;24(12):1799-1812.

van Heeswijk R, Garg V, Vandevoorde A, Witek J, Dannemann B. The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). September 17-20, 2011a; Chicago, IL.

van Heeswijk R, Vandevoorde A, Boogaerts G et al. Pharmacokinetic interactions between ARV agents and the investigational HCV protease inhibitor TVR in healthy volunteers [Abstract 119]. 18th Conference on Retroviruses and Opportunistic Infections (CROI). February 27-March 2, 2011b; Boston, MA.

Vermeersch P, Van RM, Lagrou K. Validation of a strategy for HCV antibody testing with two enzyme immunoassays in a routine clinical laboratory. *J Clin Virol*. 2008;42(4):394-398.

Vourvahis M, Plotka A, Kantaridis C, Fang A, Heera J. The effect of boceprevir and telaprevir on the pharmacokinetics of maraviroc: an open-label, fixed-sequence study in healthy volunteers [Abstract O-17]. 14th International Workshop on Clinical Pharmacology of HIV Therapy. April 22-24, 2013; Amsterdam, Netherlands.

Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518-526.

Wandeler G, Gsponer T, Bregenzer A, et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. *Clin Infect Dis*. 2012;55(10):1408-1416.

Ward JW. Testing for HCV: the first step in preventing disease transmission and improving health outcomes for HCV-infected individuals. *Antivir Ther*. 2012;17(7 Pt B):1397-1401.

Westin J, Lagging LM, Spak F, et al. Moderate alcohol intake increases fibrosis progression in untreated patients with hepatitis C virus infection. *J Viral Hepat*. 2002;9(3):235-241.

Whitlock EP, Polen MR, Green CA, Orleans T, Klein J. Behavioral counseling interventions in primary care to reduce risky/harmful alcohol use by adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2004;140(7):557-568.

Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. 1998;28(3):805-809.

Williams IT, Bell BP, Kuhnert W, Alter MJ. Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006. *Arch Intern Med*. 2011;171(3):242-248.

Witt MD, Seaberg EC, Darilay A, et al. Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis, 1984-2011. *Clin Infect Dis*. 2013;57(1):77-84.

Zarski JP, Bohn B, Bastie A, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. *J Hepatol*. 1998;28(1):27-33.

Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med*. 2011;364(25):2417-2428.

Zeuzem S, Berg T, Gane E, et al. Simeprevir Increases Rate of Sustained Virologic Response Among Treatment-Experienced Patients with HCV Genotype-1 Infection: a Phase IIb Trial. *Gastroenterology*. 2013a.

Zeuzem S, Dusheiko GM, Salupere R. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial. Hepatology: Special Issue: The 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013. Nov 1-5, 2013, 10-15-2013b;733A; Washington, DC.

Chronic Hepatitis C Virus (HCV) Infection:

Treatment Considerations from the Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health

(March 27, 2014; data last reviewed on March 6, 2014)

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I. Summary Table and Summary Figure

This document is intended to supplement the Veterans Affairs (VA) Pharmacy Benefits Management (PBM) Criteria For Use documents for HCV antivirals (available at: PBM Criteria For Use Documents). Information in this document may be used to support treatment decisions based on the existing PBM Criteria For Use documents. The following treatment considerations are based on available medical evidence and represent the opinion of an expert panel of VA HCV clinicians. The purpose of this document is to provide a detailed algorithmic approach to assist in clinical decision-making on HCV treatment considerations based on specific patient characteristics including genotype, treatment history, presence of cirrhosis, and interferon eligibility. The practitioner should interpret these treatment considerations in the clinical context of the individual patient. The content of this document is dynamic and will be revised periodically as new information becomes available. For considerations regarding patient selection for hepatitis C antiviral therapy, refer to Table 2 below.

Summary Table: Treatment Considerations and Choice of Regimen for HCV-Monoinfected and HIV/HCV-Coinfected Patients

HCV Genotype	Treatment History	Cirrhosis Status	IFN Eligibility	Preferred Regimen	Alternative Regimen	Defer for Future Treatment
1	Naïve	Non-cirrhotic or Cirrhotic	Eligible	Sofosbuvir + PEG-IFN/RBV x 12 weeks	Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks *(Do not use in GT1a with Q80K polymorphism)*	Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease
		Non-cirrhotic	Ineligible	Sofusbuvir + RBV x 24 weeks OR Sofosbuvir + Simeprevir ± RBV x 12 weeks; **NOT FDA approved**		
		Cirrhotic	Ineligible	Sofosbuvir + Simeprevir ± RBV x 12 weeks; **NOT FDA approved**		
	Experienced	Non-cirrhotic	Eligible	Sofosbuvir + PEG-IFN/RBV x 12 weeks	Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks (relapsers) or 48 weeks (prior partial or null responders) *(Do not use in GT1a with Q80K polymorphism or previous failure of boceprevir- or telaprevir-based therapy)*	Reasonable to defer if no significant extra-hepatic disease
	Experienced	Cirrhotic	Eligible	Sofosbuvir + PEG-IFN/RBV x 12 weeks	PEG-IFN/RBV null responders: Sofosbuvir + Simeprevir ± RBV x 12 weeks **NOT FDA approved**	
		Non-cirrhotic or Cirrhotic	Ineligible	Sofosbuvir + Simeprevir ± RBV x 12 weeks **NOT FDA approved**		Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease
2	Naïve	Non-cirrhotic or Cirrhotic	Either	Sofusbuvir + RBV x 12 weeks		Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease

HCV Genotype	Treatment History	Cirrhosis Status	IFN Eligibility	Preferred Regimen	Alternative Regimen	Defer for Future Treatment
	Experienced	Non-cirrhotic or Cirrhotic	Eligible	Sofosbuvir + RBV x 12-16 weeks OR Sofosbuvir + PEG-IFN/ RBV x 12 weeks; **NOT FDA approved**		Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease
			Ineligible	Sofosbuvir + RBV x 12-16 weeks		
3	Naïve	Non-cirrhotic or Cirrhotic	Eligible	Sofosbuvir + RBV x 24 weeks	Sofosbuvir + PEG-IFN/RBV x 12 weeks **NOT FDA approved**	Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease
		Non-cirrhotic or Cirrhotic	Ineligible	Sofosbuvir + RBV x 24 weeks		
	Experienced	Non-cirrhotic	Either	Sofosbuvir + RBV x 24 weeks	Sofosbuvir + PEG-IFN/RBV x 12 weeks **NOT FDA approved**	Reasonable to defer if no significant extra-hepatic disease
		Cirrhotic	Eligible	Sofosbuvir + PEG-IFN/ RBV x 12 weeks **NOT FDA approved**		
			Ineligible	Sofosbuvir + RBV x 24 weeks		
1, 2, 3, or 4	Either	Hepatocellular carcinoma	Either	Sofosbuvir + RBV x 24-48 weeks or until liver transplant, whichever occurs first		

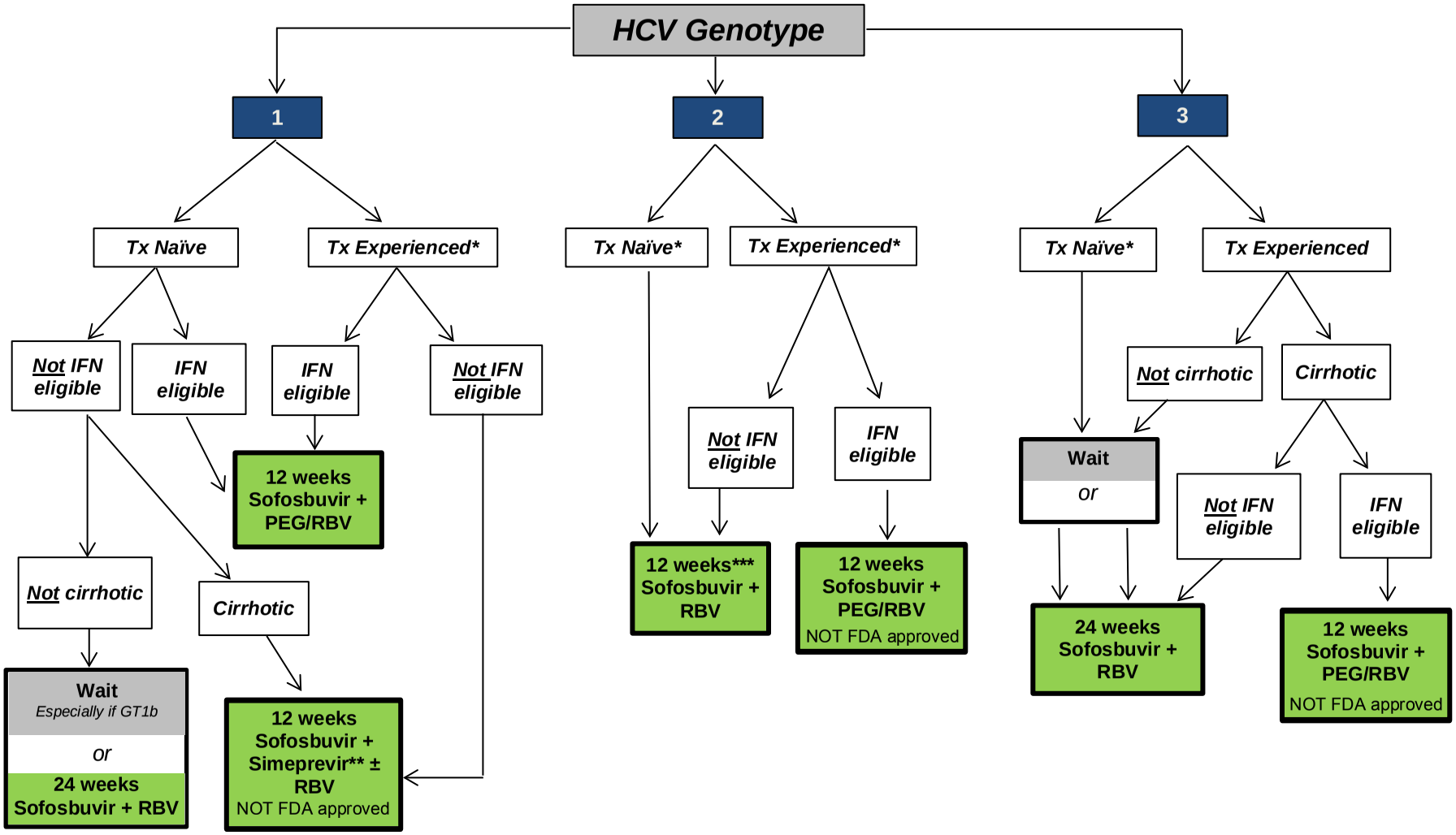
Abbreviations: PEG-IFN = peginterferon; RBV = ribavirin

Dosages: PEG-IFN alfa-2a 180 mcg subcutaneously weekly or PEG-IFN alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; simeprevir 150 mg orally daily with food; sofosbuvir 400 mg orally daily

Note: Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued.

*** Interferon ineligible or intolerant criteria:** Platelet count <75,000/mm^3; Decompensated liver cirrhosis (Child-Turcotte-Pugh (CTP) Class B or C, CTP score ≥7); Severe mental health conditions that may be exacerbated by interferon and/or respond poorly to medical therapy (with risks of interferon use documented by Mental Health evaluation); Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation; Inability to complete a prior treatment course due to documented interferon-related adverse effects (Table 5)

Summary Figure: Preferred Treatment Approach for HCV-Monoinfected and HIV/HCV-Coinfected Patients



Abbreviations: PEG-IFN = peginterferon; RBV = ribavirin; Tx = treatment

Dosages: PEG-IFN alfa-2a 180 mcg subcutaneously weekly or PEG-IFN alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; simeprevir 150 mg orally daily with food; sofosbuvir 400 mg orally daily

* Regardless of cirrhosis; ** GT1a with Q80K polymorphism may be associated with lower SVR; *** 16 weeks of sofosbuvir/ribavirin in treatment-experienced cirrhotics may improve SVR

Interferon (IFN) ineligible or intolerant criteria: Platelet count <75,000/mm^3; Decompensated liver cirrhosis (Child-Turcott-Pugh (CTP) Class B or C, CTP score ≥7); Severe mental health conditions that may be exacerbated by interferon and/or respond poorly to medical therapy (with risks of interferon use documented by Mental Health evaluation); Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation; Inability to complete a prior treatment course due to documented interferon-related adverse effects (Table 5).

I. Introduction

Successful antiviral treatment of chronic hepatitis C virus (HCV) infection is defined as a sustained virological response (SVR), and achieving an SVR significantly decreases the risk of disease progression to cirrhosis, liver cancer, liver failure, and death. The Veterans Health Administration (VHA) expects to treat all Veterans with chronic hepatitis C virus (HCV) infection who wish to be treated and are suitable for treatment. Furthermore, the VHA will use the optimal drug treatments available, after analysis of efficacy, safety, and costs. Providing appropriate treatment to Veterans requires time, expertise including coordination with other services (e.g., Primary Care, Mental Health, Pharmacy, Social Work), and funding.

The following treatment considerations summarize the current best practices in the management and treatment of chronic hepatitis C virus (HCV) infection within the VHA, including the use of interferon-based and interferon-free regimens. These considerations are based on an extensive review of published data, American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) Recommendations for Testing, Managing, and Treating Hepatitis C (www.hcvguidelines.org), publicly available reviews from the U.S. Food and Drug Administration (FDA) data that are currently in abstract form, and input from VHA thought leaders involved in the care of Veterans with HCV infection.

Limitations: There are important limitations in the design of most studies of direct acting antiviral (DAA) agents in the treatment of hepatitis C. These limitations include: 1) small sample sizes, with resultant wide confidence intervals for sustained virologic response (SVR); 2) inclusion of few patients with cirrhosis, especially advanced cirrhosis; 3) lack of a control arm in most studies; 4) lack of head-to-head trials of DAA regimens; 5) many studies were open-label and no studies were double blinded; 6) most trials excluded patients with chronic hepatitis B virus infection (HBV), human immunodeficiency virus infection (HIV), cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and alcohol use; 7) studies do not yet have follow up data to report on long-term virologic and clinical outcomes from DAAs. Finally, much of the existing data is from abstracts and not published in peer-reviewed publications. With the limitations mentioned above, the committee weighs the strength and weaknesses of the existing data, recognizes there are gaps in the evidence, yet often needs to make decisions based on suboptimal data. The content in the document will change as new data become available. Some of the limitations of studies are noted in the "Comments" column in the tables. Overall, caution about the application of preliminary data should be exercised until detailed complete results become available.

Grading the Evidence: Treatment considerations were developed using systematic weighting and grading of the quality of evidence according to criteria used in the U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (Table 1). Each panel member participated in the preparation and review of the draft recommendations and the committee approved, with the consensus statements reflected in the final document. The final recommendations were reviewed and endorsed by the VHA Office of Public Health. Additional resources pertaining to the care of the HCV-infected patient are available at www.hepatitis.va.gov.

Table 1. Grading System

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B: Moderate recommendation for the statement** **C: Optional recommendation for the statement**	**I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints** **II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes** **III. Expert opinion**

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Page A-3, Table 2. Accessed March 25, 2014.

Clinical benefit of achieving SVR (i.e., cure): SVR, defined as undetectable HCV RNA levels at least 12 weeks after completion of treatment, is the primary endpoint of successful therapy. There is documented concordance of SVR at 12 and 24 weeks (referred to as SVR12 and SVR24, respectively) with reported positive and negative predictive values upward of 98% in boceprevir- and telaprevir-based studies. The agreement between SVR12 and SVR24 is related to the timing of virologic relapse and the finding that ≥98% of relapses occur within the first 12 weeks after treatment cessation. Based on these data, the FDA now recommends SVR at 12 weeks after completion of treatment as the primary endpoint for HCV clinical trials.[1,2,3]

Achieving an SVR with peginterferon/ribavirin treatment improves clinical outcomes, such as improving blood tests of liver function, lowering the risk of progressing to decompensated cirrhosis or HCC, and prolonging life. Liver fibrosis may improve (regress) after achieving an SVR. Patients with cirrhosis who achieve an SVR also have reduced progression of their liver disease and reduced risk of HCC. Thus, there is compelling evidence that curing patients, including patients with cirrhosis, of HCV infection has clinically meaningful improvements in liver function and overall health.

Principles for patient selection for HCV treatment: The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver transplant recipients. Urgent antiviral treatment should be considered in patients with advanced cirrhosis, selected patients with HCC awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV. Patients with mild liver disease (METAVIR F0-2) may consider waiting for additional FDA-approved, interferon-free regimens that are expected to attain high SVR with low adverse effect profile. Approval of such regimens is anticipated over the next 12 to 24 months. Decisions regarding deferral of treatment also should take into account the lack of data regarding the real-world safety and effectiveness of recently approved DAAs.

Patient adherence: Evaluating a patient's adherence to medical recommendations and the prescribed regimen is crucial to the patient selection process. Factors that may complicate adherence, such as active substance abuse, neurocognitive disorders, and lack of social support, should be noted and adequately

addressed before initiating medications. Providers should incorporate strategies for measuring and supporting adherence within their clinics.

Table 2. Considerations for Selecting Chronic HCV-Infected Patients for Treatment

Liver Disease Category	Considerations	Evidence Grade
No cirrhosis	Consider waiting until better treatments are available. Future treatments are likely to have fewer side effects, shorter duration, higher efficacy, and lower pill burden.	B-III
Compensated cirrhosis	Treatment is recommended for appropriate patients with compensated cirrhosis. Refer to Table 13, "Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates," for guidance on diagnosis of cirrhosis.	B-III
Decompensated cirrhosis, defined by one of the following: CTP score ≥7, ascites, hepatic encephalopathy, variceal bleeding or jaundice	Treatment options are limited and the risk versus benefits of treatment must be carefully considered. Consult a specialist with experience in management of HCV.	A-II
Hepatocellular carcinoma (HCC)	Consider treatment for patients in whom HCC treatment is potentially curative, including selected patients on the liver transplant list.	A-II
Post-transplant recipients with cirrhosis	Risk versus benefits of treatment must be carefully considered. Consult a specialist with experience in management of HCV.	A-II
Patients with serious extra-hepatic manifestations of HCV	Patients with serious extra-hepatic manifestations of HCV, such as leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, or symptomatic cryoglobulinemia despite mild liver disease should receive treatment as soon as possible. Consult a specialist with experience in management of HCV.	A-III

CTP = Child-Turcotte-Pugh

Deciding when a patient should wait for future treatment: Deferral of HCV treatment may be considered in some patients until newer therapies are available that might further optimize the chance of treatment success and reduce the potential for treatment-related adverse effects (Table 3). Such patients include those without cirrhosis. Patients who have cirrhosis generally are recommended for treatment sooner rather than later, to reduce their risk of decompensation or development of HCC.

Table 3. Factors to Consider in Deciding to Treat Chronic HCV or Wait for Availability of Newer Therapies

Factor	Comment
Stage of liver fibrosis	Patients with mild liver fibrosis (METAVIR F0 – F2) are unlikely to develop decompensated liver disease in the subsequent few years and might benefit from waiting for approval of additional safe and effective interferon-free regimens.
Intolerance or contraindications to interferon	Future interferon-free regimens are expected to have fewer adverse events, be less complex to administer, and have high SVR rates. Interferon-free regimens are expected to receive FDA approval in late 2014.
Intolerance or contraindication to ribavirin	Ribavirin-free regimens have achieved high SVR rates in Phase II and Phase III trials and may be approved by the FDA in late 2014 for treatment of HCV genotype 1 infection.
Adherence	Future treatments may be less complex (e.g., one or a few pills per day), potentially increasing adherence.
Treatment duration	Future treatment duration is likely to be 12 weeks or less for most patients.
SVR	Future therapies may result in higher SVR rates in select groups (e.g., cirrhotics, patients who failed boceprevir- or telaprevir-based therapy).
Lack of adequate data	Key groups (e.g., patients who have failed boceprevir- or telaprevir-based therapy, decompensated cirrhotics) have not been well studied, and SVR rates in selected patient groups are based on modeling.

Future treatments: Multiple new drugs are being tested in patients with HCV, and preliminary evidence from several Phase II and III trials suggest excellent efficacy (>90% SVR for all genotypes), excellent safety profile, and interferon-free regimens for all genotypes. Thus, a variety of treatment options are expected to become available for HCV patients in the foreseeable future. When new drugs gain adequate evidence and/or receive FDA approval, preferred treatment regimens may change. The contents of this documentwill be updated as new treatments become available. Informing Veterans that a variety of highly effective, well-tolerated, interferon-free treatments with short treatment durations will be available relatively soon should be a priority.

Patient identification: A population health-based approach for selection of patients for treatment should be considered. The HCV Clinical Case Registry (CCR) (vaww.vistau.med.va.gov/VistaU/ccr/default.htm) is available at each VA facility and is accessible to selected clinicians by request. Using the CCR, providers can generate facility specific reports on the numbers and names of patients with HCV stratified by cirrhosis (determined fibrosis markers such as by platelet count, FIB-4, APRI), genotype, prior treatment experience, and other clinical considerations. The availability and customizability of the information obtained from local CCR reports can optimize identification of patients in urgent need of treatment.

Pre-treatment evaluation: Before initiating antiviral therapy in a patient with chronic HCV, the information listed in Table 4 should be assessed.

Table 4. Pre-Treatment Evaluation

Essential pre-treatment information*
• HCV genotype (including subtype, e.g. 1a or 1b)   - Q80K polymorphism IF genotype 1a AND considering simeprevir/peginterferon/ribavirin therapy • Clinical assessment of cirrhosis or no-cirrhosis • If cirrhotic, exclusion of hepatocellular carcinoma based on imaging study within the past 6 months • Previous HCV treatment history and outcome • Interferon eligibility (see Table 5 below) • HIV status and if HIV +, current antiretroviral regimen and degree of viral suppression • Documented use of 2 forms of birth control in patient and sexual partners in whom a ribavirin-containing regimen is chosen

* For further guidance on pretreatment assessment and laboratory monitoring, refer to the *2012 Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office*. (www.hepatitis.va.gov/provider/guidelines/2012HCV-pretreatment-assessments.asp)

Interferon eligibility: Although clinical trial data for new HCV treatment regimens that include both peginterferon and ribavirin are more robust, some patients are not able to tolerate interferon or are ineligible and should be considered for treatment with an interferon-free regimen. The following criteria should be used to determine whether a patient is considered to be interferon ineligible or intolerant (Table 5).

Table 5. Interferon Ineligible or Intolerant Criteria

• Platelet count <75,000/mm^3 • Decompensated liver cirrhosis (Child-Turcotte-Pugh Class B or C, CTP score ≥7) • Severe mental health conditions that may be exacerbated by interferon or respond poorly to medical therapy (with risks of interferon use documented by Mental Health evaluation) • Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation • Inability to complete a prior treatment course due to documented interferon-related adverse effects

III. Chronic HCV Genotype 1 Infection

Table 6. Genotype 1, Interferon Eligible: Preferred Regimens and SVR Rates from Supporting Data

Regimens with optimal efficacy, favorable tolerability and toxicity profile, and ease of use.

Treatment Considerations					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
Naïve GT1a or 1b	Non-cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-II	89% (261/292)[a] Stratified by GT: GT1a: 92% (206/225)[a] GT1b: 82% (54/66)[a] (represents non-cirrhotic and cirrhotic patients; 1 patient had GT 1a/1b)	Reasonable to defer for future treatment if no significant extra-hepatic disease.
	Cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-II	80% (43/54)[a]	SVR in cirrhotics was not stratified by GT1a and GT1b.
Experienced GT1a or 1b	Non-cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-III	No data; estimated to be 71%-78%[b]	Reasonable to defer for future treatment if no significant extra-hepatic disease. **SVR estimates based on FDA modeling in treatment-naïve patients with poor predictors.**
	Cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-III	No data; estimated to be 71%[b]	**SVR estimates based on FDA modeling in treatment-naïve patients with poor predictors.**

[a] NEUTRINO[4]

[b] www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204671Orig1s000SumR.pdf;

PEG-IFN = Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV = Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; Sofosbuvir 400 mg orally daily. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Table 7. Genotype 1, Interferon Ineligible or Intolerant*: Preferred Regimens and SVR Rates from Supporting Data

Regimens with optimal efficacy, favorable tolerability and toxicity profile, and ease of use. SVR rates cannot be compared between trials because of differences in study populations and clinical trial methodology.

Treatment Considerations					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
Naïve GT1a or 1b	Non-cirrhotic	Sofosbuvir + RBV	24 weeks	B-I	24-week duration: 53% (10/19)[a] 90% (9/10)[b] 12-week duration: 47% (9/19)[a] 84% (21/25)[c]	Reasonable to defer for future treatment if no significant extra-hepatic disease, especially in GT1b-infected patients. The largest clinical trial to date of sofosbuvir/ribavirin therapy was conducted in 114 patients with HIV/HCV coinfection. Among GT1b-infected patients with HIV/HCV coinfection, SVR was achieved in 54% (13/24) as compared with 82% (74/90) with GT1a infection.[d] There is wide variability in SVR rates (53-90% with 24 weeks of treatment) based on small studies in HCV-monoinfected patients.[a,b,c]
		Sofosbuvir + Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-III	Data not available	Reasonable to defer treatment if no significant extra-hepatic disease. Preferred regimen based on data in treatment-naïve METAVIR F3/F4 patients, in which 100% (19/19) of patients achieved SVR4.[e] GT1a: Q80K polymorphism may theoretically increase risk of relapse and thus, reduce achievement of SVR.

Treatment Considerations					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
	Cirrhotic	Sofosbuvir + Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-II	SVR4: 100% (12/12, +RBV)[e] [95% CI: 74-100] SVR4: 100% (7/7, -RBV)[e] [95% CI: 59-100] With Q80K polymorphism: SVR4: 91% (10/11)[e] (includes treatment-naïve and treatment-experienced patients) [95% CI: 59-100]	Small sample size, preliminary data. **DO NOT USE sofosbuvir + ribavirin in cirrhotics due to insufficient data.**
Experienced GT1a or 1b	Non-cirrhotic	Sofosbuvir + Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-II	96% (26/27, +RBV)[e] [95% CI: 81-100] 93% (13/14, -RBV)[e] [95% CI: 66-100] Null responders with Q80K polymorphism: 89% (24/27)[e] [95% CI: 71-98]	Small sample size. Reasonable to defer for future treatment if no significant extrahepatic disease. **DO NOT USE sofosbuvir + ribavirin in treatment-experienced patients due to insufficient data**
	Cirrhotic	Sofosbuvir + Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-II	SVR4: 93% (14/15, +RBV)[e] [95% CI: 68-100] SVR4: 100% (7/7, -RBV)[e] [95% CI: 59-100] With Q80K polymorphism: SVR4: 91% (10/11)[e] (includes treatment-naïve and treatment-experienced patients) [95% CI: 59-100]	Small sample size, preliminary data. Preferred regimen based on data in null responders with METAVIR F3/F4. **DO NOT USE sofosbuvir + ribavirin in treatment-experienced patients due to insufficient data.**

SVR4 = undetectable HCV RNA levels at 4 weeks posttreatment; 95% CI: 95% confidence interval for binomial proportion
[a] QUANTUM[11], [b] NIH-SPARE[10], [c] ELECTRON[12], [d] PHOTON-1[9], [e] COSMOS[8]; RBV = Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; Simeprevir 150 mg orally daily with food; Sofosbuvir 400 mg orally daily. Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued.
***Interferon ineligible or intolerant criteria:** See Table 5.

Table 8. Genotype 1, Interferon Eligible: Alternative Regimens and SVR Rates from Supporting Data

Regimens may be effective and tolerable, but have potential disadvantages when compared with preferred regimens. SVR rates cannot be compared between trials.

Treatment Considerations				Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**	**Evidence grade**	**SVR% (N/N)**	**Comments**
Naïve GT1a *without Q80K* Or GT1b	Non-cirrhotic	Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks	B-I	84% (317/378)[a] Stratified by GT: GT1a: w/o Q80K: 84% (138/165)[a] with Q80K: 58% (49/84)[a] GT1b: 85% (228/267)[a]	Reasonable to defer for future treatment if no significant extrahepatic disease. *Screen for Q80K polymorphism prior to treatment.* **DO NOT USE simeprevir/PEG-IFN/RBV in GT1a patients who have the Q80K polymorphism.**
	Cirrhotic	Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks	C-I	68% (89/130)[a] F3: 73% (60/82)[a] F4: 60% (29/48)[a]	*Screen for Q80K polymorphism prior to treatment.* **DO NOT USE simeprevir/PEG-IFN/RBV in GT1a patients who have the Q80K polymorphism.**
Experienced GT1a *without Q80K* Or GT1b	Non-cirrhotic	***PEG-IFN/RBV Relapsers:*** Simeprevir x 12 weeks + PEG-IFN/ RBV x 24 weeks ***PEG-IFN/RBV Partial and Null Responders:*** Simeprevir x 12 weeks + PEG-IFN/ RBV x 48 weeks	B-I	Relapsers: 82% (137/167)[b] Partial Responders: 65% (15/23)[c] GT1a: 56% (14/25) GT1b: 88% (38/43) Nulls: 53% (9/17)[c] GT1a:42% (11/26) GT1b: 58% (14/24)	Reasonable to defer for future treatment if no significant extrahepatic disease, or if **PEG-IFN/RBV partial or null responder.** *Screen for Q80K polymorphism prior to treatment.* **DO NOT USE simeprevir/PEG-IFN/RBV in GT1a patients who have the Q80K polymorphism.** **DO NOT USE if *previously failed a boceprevir- or telaprevir-based regimen.***
	Cirrhotic	***PEG-IFN/RBV Relapsers:***	B-I	Relapsers: 74% (29/39)[b]	*Screen for Q80K polymorphism prior to*

Treatment Considerations				Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**	**Evidence grade**	**SVR% (N/N)**	**Comments**
		Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks ***PEG-IFN/RBV Partial and Null Responders:*** Simeprevir x 12 weeks + PEG-IFN/RBV x 48 weeks		Partial Responders: 82% (9/11)[c] Nulls: 31% (4/13)[c]	*treatment.* **DO NOT USE simeprevir/PEG-IFN/RBV in GT1a patients who have the Q80K polymorphism.** **DO NOT USE in cirrhotic null responders OR in patients who have previously failed a boceprevir- or telaprevir-based regimen.**
	Cirrhotic	***PEG-IFN/RBV Null Responders:*** Sofosbuvir + Simeprevir ± RBV x 12 weeks **NOT FDA approved**	B-II	SVR4: 93% (14/15,+RBV)[d] [95% CI: 68-100] SVR4: 100% (7/7, –RBV)[d] [95% CI: 59-100] Null responders with Q80K polymorphism: SVR4: SVR 91% (10/11)[d] [95% CI: 69-100]	Small sample size, preliminary data. Preferred regimen based on data in null responders with METAVIR F3/F4.

95% CI: 95% confidence interval for binomial proportion; [a] QUEST 1 & 2[5], [b] PROMISE[6], [c] ASPIRE[7], [d] COSMOS[8]; PEG-IFN = Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV = Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; Simeprevir 150 mg orally daily with food. Simeprevir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued. For definitions of treatment response, refer to the *2012 Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office* (www.hepatitis.va.gov/provider/guidelines/2012HCV-definitions-of-response.asp).

Interferon-Containing Regimens in Genotype 1 – Sofosbuvir

Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75 kg and 1,200 mg/day if ≥75 kg with food, in divided doses) and peginterferon for 12 weeks is FDA approved for treatment-naïve and treatment-experienced patients with chronic HCV genotype 1 or 4 infection. (See Table 6.)

The high SVR rates demonstrated or expected (based on FDA modeling) in the GT1 population irrespective of baseline characteristics, ease of use, and short treatment duration provide sufficient evidence to recommend sofosbuvir/peginterferon/ribavirin for 12 weeks as the preferred treatment regimen for HCV GT1 infection.

Sofosbuvir has been evaluated in a Phase III, open-label, single-arm clinical trial of monoinfected, treatment-naïve GT1-infected patients in combination with peginterferon and ribavirin for 12 weeks (NEUTRINO, n=327). No comparator arm with only peginterferon plus ribavirin was included in this study; rather, superiority of the sofosbuvir regimen was determined from historical response rates. SVR rates were 92% for GT1a, 82% for GT1b, 92% in those without cirrhosis, 80% in those with cirrhosis, 87% in blacks, 91% in non-blacks, 98% in those with IL28B CC, and 87% in those with IL28B non-CC alleles.[4] In those with multiple baseline factors traditionally associated with a lower treatment response (METAVIR F3/F4 fibrosis, IL28B non-CC, and HCV RNA >800,000IU/mL), SVR rates were 71%. Clinical trials of sofosbuvir were not conducted in treatment-experienced GT1-infected patients. Nevertheless, the FDA approved sofosbuvir/peginterferon/ribavirin for 12 weeks for treatment-experienced patients based on modeling that suggested an SVR rate of 71-78% in this group (www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204671Orig1s000SumR.pdf).

The 12-week treatment duration for sofosbuvir/peginterferon/ribavirin is significantly shorter than that for other regimens available at this time, and it is expected to be better tolerated with a more favorable adherence profile. Furthermore, sofosbuvir is associated with fewer side effects and fewer drug interactions, though DAAs have not been compared head-to-head in any clinical trials at this time. Sofosbuvir also is active against NS3/4A protease inhibitor-, NS5B non-nucleoside inhibitor- and NS5A inhibitor-resistant variants.

Interferon-Containing Regimens in Genotype 1 – Simeprevir

Simeprevir (150 mg/day with food) for 12 weeks in combination with peginterferon/ribavirin (1,000 mg/day if <75 kg and 1,200 mg/day if ≥75 kg with food, in divided doses) for 24 weeks is FDA approved for treatment-naïve patients and treatment-experienced relapsers with chronic HCV genotype 1 infection. (See Table 8.)

Simeprevir (150 mg/day with food) for 12 weeks in combination with peginterferon/ribavirin for 48 weeks is FDA approved for treatment-experienced partial and null responders with chronic HCV genotype 1 infection. (See Table 8.)

Simeprevir is an acceptable alternative treatment for GT1-infected patients without the baseline Q80K polymorphism in the HCV NS3/4a polymerase. From clinical studies with simeprevir plus peginterferon/ribavirin, 48% of U.S.-enrolled patients with GT1a harbored the Q80K polymorphism at baseline, which was associated with reduced SVR rates in these patients. Screening for the Q80K polymorphism prior to treatment is strongly recommended for patients infected with GT1a, and simeprevir plus peginterferon/ribavirin therapy should not be used in those with the Q80K polymorphism. For patients who will receive simeprevir/sofosbuvir therapy, Q80K polymorphism testing prior to treatment is strongly recommended but not required.

Simeprevir has been evaluated in clinical trials of treatment-naïve patients and treatment-experienced patients (relapsers and partial and null responders to peginterferon/ribavirin). In treatment-naïve patients, SVR rates were higher with simeprevir/peginterferon/ribavirin in those with GT1b versus GT1a

(85% vs 75%), IL28b CC versus CT or TT (95% vs 78% or 61%, respectively), and non-cirrhotics versus cirrhotics (84% vs 60-65%, respectively). SVR rates were lower in GT1a-infected patients who had the Q80K polymorphism at baseline compared with those without it (58% and 84%, respectively).[5] Among peginterferon/ribavirin relapsers, SVR rates with simeprevir-based therapy were 82% in those with METAVIR F0-2 (compared with 41% in those receiving peginterferon/ribavirin) and 73% with METAVIR F3-4 (compared with 41% and 24% in those receiving peginterferon/ribavirin, respectively).[6] Among peginterferon/ribavirin partial responders receiving simeprevir plus peginterferon/ribavirin for 12 weeks followed by peginterferon/ribavirin for an additional 36 weeks, the SVR rate was 65% (15/23). The SVR rates from pooled simeprevir duration groups in partial responders with GT1a and GT1b subtypes were 56% (14/25) and 88% (38/43), respectively. Simpeprevir-based therapy in cirrhotic, peginterferon/ribavirin partial responders achieved an SVR in 82% (9/11). In peginterferon/ribavirin null responders receiving simeprevir plus peginterferon/ribavirin for 12 weeks followed by peginterferon and ribavirin for an additional 36 weeks, the SVR rate was 53% (9/17). The SVR rates from pooled simeprevir duration groups in null responders with GT1a and GT1b subtypes were 42% (11/26) and 58% (14/24), respectively. Simeprevir-based therapy in cirrhotic, peginterferon/ribavirin null responders attained SVR in 31% (4/13).[7]

For definitions of treatment response, refer to the *2012 Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office* (www.hepatitis.va.gov/provider/guidelines/2012HCV-definitions-of-response.asp).

The pharmacology (drug-drug interactions, food requirement), resistance profile, and more complicated regimen, which involves a longer duration of peginterferon/ribavirin treatment (24-48 weeks depending on baseline patient characteristics), makes this regimen more complicated and less desirable.

Interferon-Free Regimens in Genotype 1 – Sofosbuvir/Simeprevir and Sofosbuvir/Ribavirin

Based on limited data with sofosbuvir/simeprevir, and lower SVR rates with sofosbuvir/ribavirin, an interferon-free regimen should be used only to urgently treat Veterans with documented interferon ineligibility or intolerance in whom delaying therapy would have a high likelihood of resulting in morbidity and mortality. (See Table 7.)

Based on preliminary data, sofosbuvir/simeprevir may be considered as the preferred regimen in GT1-infected patients who are interferon ineligible or intolerant and as an alternative regimen in interferon eligible, cirrhotic null responders to prior peginterferon/ribavirin. This combination currently is not approved by the FDA.

Sofosbuvir/Simeprevir

The combination of sofosbuvir/simeprevir ± ribavirin has been evaluated in a limited population of GT1-infected patients in an ongoing open-label, Phase IIa trial (COSMOS); data from COSMOS have not been audited or reviewed by FDA. In 41 null responders with METAVIR F0-F2, SVR rates were 96% and 93% with 12 weeks of sofosbuvir/simeprevir with and without ribavirin, respectively. In patients with METAVIR F3-F4, SVR4 rates in 22 null responders were 93% and 100% with 12 weeks of sofosbuvir/simeprevir with and without ribavirin, respectively, and the SVR4 rate in 19 treatment-naïve patients was 100%. All relapses occurred in patients with GT1a and the Q80K polymorphism; relapse occurred in 3 null responders with METAVIR F0-F2 and 1 patient in the cohort with METAVIR F3/F4.[8]

Sofosbuvir/Ribavirin

FDA labeling identifies sofosbuvir/ribavirin (without peginterferon) for 24 weeks as a potential consideration for GT1-infected patients who are ineligible to receive an interferon-based regimen; however, limited data exist for GT1 treatment-experienced patients and those with cirrhosis. SVR rates for this regimen were extrapolated from several clinical trials. The largest trial of sofosbuvir/ribavirin was a Phase III study (PHOTON-1) of 114 treatment-naïve, GT1-infected patients with HIV/HCV coinfection. SVR rates were 82% in those with GT1a, 54% in those with GT1b, 80% in those with IL28B CC, and 75% in those with IL28B non-CC alleles. Relapse accounted for the majority of treatment failures. Of note, only 4% of GT1-infected patients in PHOTON-1 had cirrhosis.[9] In a small National Institutes of Health study of an inner-city population consisting of 10 treatment-naïve GT1-infected patients without cirrhosis who received sofosbuvir and weight-based ribavirin for 24 weeks, SVR was achieved in 90% (9/10); in the same study, among 25 treatment-naïve patients with unfavorable traditional predictors of treatment response and any stage of liver fibrosis, SVR was achieved in 68% (17/25; 1 patient dropped out at week 3 of treatment).[10] Another small study of mostly white, IL28B-CC, treatment-naïve patients without cirrhosis and normal body mass index, SVR was achieved in 84% (21/25) with a 12-week sofosbuvir/ribavirin regimen. An evaluation of a 12- and 24-week sofosbuvir/ribavirin regimen in 50 mostly non-CC, treatment-naïve patients of mixed ethnicity reported SVR rates of 56% (14/25) and 52% (13/25), respectively.[11] The only available data for sofosbuvir/ribavirin in treatment-experienced patients are from 10 null responders who were treated for 12 weeks in a comparator arm of the ELECTRON trial, which reported an SVR of 10% (1/10).[12] Based on modest SVR rates along with the lack of data in cirrhotics and treatment-experienced patients in these studies, sofosbuvir/ribavirin use is not recommended for cirrhotics and treatment-experienced patients.

Genotype 1-Infected Patients Who Failed Treatment with a Boceprevir- or Telaprevir-Based Regimen

There are insufficient data on the use of sofosbuvir- or simeprevir-based therapy in patients who have failed treatment with boceprevir- or telaprevir-based therapy. Due to concerns of potential cross-resistance, a simeprevir-based regimen should be avoided in patients who have previously failed a boceprevir- or telaprevir-based regimen due to lack of virologic response.

IV. Chronic HCV Genotype 2 Infection

Table 9. Genotype 2: Preferred Regimens in HCV Monoinfection and HIV/HCV Coinfection, and SVR Rates from Supporting Data

Regimens with optimal efficacy, favorable tolerability and toxicity profile, and ease of use. SVR rates cannot be compared between trials.

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR (N/N)**	
Naïve GT2	Non-cirrhotic	Sofosbuvir + RBV	12 weeks	A-I	97% (59/61)[a] 92% (85/92)[b] 97% (29/30)[c]	Reasonable to defer for future treatment if no significant extrahepatic disease.
	Cirrhotic	Sofosbuvir + RBV	12 weeks	A-II	83% (10/12)[a] 94% (16/17)[b] 100% (2/2)[c]	
Experienced GT2	Non-cirrhotic	Sofosbuvir + RBV	12 weeks	A-II	91% (30/33)[c] Relapsers: 86% (25/29)[d] Nonresponders: 70% (7/10)[d]	Reasonable to defer for future treatment if no significant extrahepatic disease.
			16 weeks	B-II	Relapsers: 89% (24/27)[d] Nonresponders: 88% (7/8)[d]	**NOT FDA approved**
		Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	B-II	100% (9/9)[f]	If interferon eligible
	Cirrhotic	Sofosbuvir + RBV	12 weeks	A-II	88% (7/8)[c] 60% (6/10)[d]	
			16 weeks	B-II	78% (7/9)[d]	**NOT FDA approved**
		Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	B-II	93% (13/14)[e]	If interferon eligible
Naïve or Experienced GT2 HIV/HCV Co-infection	Non-cirrhotic or Cirrhotic	Sofosbuvir + RBV	12 weeks	A-I	88% (23/26)[f]	Reasonable to defer for future treatment if non-cirrhotic and no

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	Cirrhosis status	Regimen and duration		Evidence grade	SVR (N/N)	
						significant extrahepatic disease. In treatment-experienced patients, sofosbuvir/ribavirin x 12-16 weeks or sofosbuvir/PEG-IFN/RBV x 12 weeks (not FDA-approved) is preferred based on SVR rates in HCV-monoinfected patients.

[a] FISSION[4], [b] POSITRON[16], [c] VALENCE[15], [d] FUSION[16], [e] LONESTAR-2[13], [f] PHOTON-1[9]; PEG-IFN = Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV = Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; Sofosbuvir 400 mg orally daily. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Table 10. Genotype 2: Alternative Regimens in HCV Monoinfection and HIV/HCV Coinfection, and SVR Rates from Supporting Data

Regimens may be effective and tolerable, but have potential disadvantages when compared with preferred regimens. SVR rates cannot be compared between trials.

Treatment Considerations					Supporting Information
Treatment history and HCV genotype (GT)	Cirrhosis status	Regimen and duration		Evidence grade	SVR (N/N)
Naïve GT2	Non-cirrhotic	Peginterferon + RBV	24 weeks	B-I	82%[a]

[a] Ghany et al.[14]; Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV = Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food.

Sofosbuvir in Genotype 2

Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75kg or 1,200 mg/day if ≥75 kg/day with food, in divided doses) for 12 weeks is FDA approved for treatment-naïve and treatment-experienced patients with chronic HCV genotype 2 infection. (See Table 9.)

The preferred treatment regimen for chronic HCV GT2 infection is supported by the results of four Phase III studies.[4,15,16] SVR rates among these four studies were >90% in treatment-naïve and non-cirrhotic populations. Patients with cirrhosis and previous nonresponse to peginterferon-containing regimens were less well represented in the studies. Among treatment-experienced patients from the VALENCE study, SVR was achieved in 91% (30/33) of non-cirrhotics and 88% (7/8) of cirrhotics with sofosbuvir/ribavirin treatment for 12 weeks.[15] In the FUSION study, a statistically insignificant increase in SVR rates was seen with extending sofosbuvir/ribavirin therapy from 12 to 16 weeks in prior nonresponders without cirrhosis (70% [7/10] vs. 88% [7/8], respectively) and in treatment-experienced cirrhotics (60% [6/10] vs. 78% [7/9], respectively).[16] Based on results from this small study, sofosbuvir and ribavirin for 16 weeks may be considered as an option in treatment-experienced patients, however, this 16-week regimen is not FDA approved . In interferon eligible, treatment-experienced patients, sofosbuvir plus peginterferon/ribavirin for 12 weeks may be considered. Among treatment-experienced non-cirrhotics and cirrhotics from the LONESTAR-2 study, SVR was achieved in 100% (9/9) and 93% (13/14), respectively, with the addition of peginterferon to sofosbuvir/ribavirin therapy for 12 weeks.[13] This regimen is not FDA approved.

Among treatment-naïve, non-cirrhotic and interferon-tolerant populations, an alternative regimen for treatment of HCV GT2 is peginterferon and ribavirin 800 mg daily for 24 weeks.[14] Pretreatment characteristics of GT2 patients who achieve a high rate of SVR (>75%) with this regimen include a low baseline HCV RNA (≤800,000 IU/mL) and absence of bridging fibrosis or cirrhosis, absence of prior treatment failure, and absence of other factors related to poor interferon responsiveness (e.g., African American ethnicity, obesity, IL28 non-CC genotype).[14] Use of weight-based ribavirin (i.e., 1,000 mg if <75 kg or 1,200 mg if ≥75 kg daily) may improve treatment outcomes or allow for a shorter treatment duration.

V. Chronic HCV Genotype 3 Infection

Table 11. Genotype 3: Preferred Regimens in HCV Monoinfection and HIV/HCV Coinfection, and SVR Rates from Supporting Data

Regimens with optimal efficacy, favorable tolerability and toxicity profile, and ease of use. SVR rates cannot be compared between trials.

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	Cirrhosis status	Regimen and duration		Evidence grade	SVR% (N/N)	
Naïve GT3	Non-cirrhotic	Sofosbuvir + RBV	24 weeks	A-I	94% (86/92)[a]	Reasonable to defer for future treatment if no significant extrahepatic disease.

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
	Cirrhotic	Sofosbuvir + RBV	24 weeks	A-I	92% (12/13)[a]	
Experienced GT3	Non-cirrhotic	Sofosbuvir + RBV	24 weeks	A-I	87% (87/100)[a]	Reasonable to defer for future treatment if no significant extrahepatic disease.
	Cirrhotic, Interferon-eligible	Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	A-II	83% (10/12)[b]	
	Cirrhotic, Interferon ineligible or intolerant*	Sofosbuvir + RBV	24 weeks	A-I	60% (27/45)[a]	
Naïve or Experienced GT3 HIV/HCV Coinfection	Non-cirrhotic or Cirrhotic	Sofosbuvir + RBV	24 weeks	A-II	92% (12/13) [c]	Reasonable to defer for future treatment if non-cirrhotic and no significant extrahepatic disease. In treatment-experienced cirrhotics who are IFN eligible, sofosbuvir/PEG-IFN/RBV x 12 weeks (not FDA approved) is preferred based on SVR rates in HCV-monoinfected patients.

[a] VALENCE[15], [b] LONESTAR-2[13], [c] PHOTON-1[9]; PEG-IFN = Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV = Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; Sofosbuvir 400 mg orally daily. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

***Interferon ineligible or intolerant criteria:** See Table 5.

Table 12. Genotype 3: Alternative Regimens in HCV Monoinfection and HIV/HCV Coinfection (Interferon-Eligible Patients), and SVR Rates from Supporting Data

Regimens may be effective and tolerable, but have potential disadvantages when compared with preferred regimens. SVR rates cannot be compared between trials.

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
Naïve GT3	Non-cirrhotic	Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	A-II	92% (23/25)[a]; represents combined GT2 and GT3 data	Reasonable to defer for future treatment if no significant extrahepatic disease.
	Cirrhotic	Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	A-III	Data not available	
Experienced GT3	Non-cirrhotic	Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	A-II	83% (10/12)[b]	Reasonable to defer for future treatment if no significant extrahepatic disease.

[a] PROTON[17], [b] LONESTAR-2[13]; PEG-IFN = Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV = Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; Sofosbuvir 400 mg orally daily. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Sofosbuvir for Genotype 3

Sofosbuvir (400 mg/day) plus ribavirin (1,000 mg/day if <75 kg or 1,200 mg if ≥75 kg with food, in divided doses) for 24 weeks is FDA approved for treatment-naïve and treatment-experienced patients with chronic HCV genotype 3 infection.

The preferred regimen for chronic HCV GT3 is supported by the results of a Phase III, randomized study (VALENCE) that evaluated treatment with sofosbuvir and ribavirin for 24 weeks in GT3 patients (n=250). In treatment-naïve patients, SVR was achieved in 94% (86/92) of non-cirrhotics and 92% (12/13) of cirrhotics. In treatment-experienced patients, SVR was attained in 87% (87/100) of non-cirrhotics and 60% (27/45) of cirrhotics.[15] In other studies, shorter treatment duration (12-16 weeks) with sofosbuvir and ribavirin resulted in lower SVR rates (21-68%).[4,9,16]

A Phase II, open-label study (PROTON) with sofosbuvir, peginterferon, and ribavirin for 12 weeks in treatment-naïve, non-cirrhotic patients achieved SVR in 92%; however, these results represent combined GT2 and GT3 data.[17] In GT3 treatment-experienced patients (n=24), a Phase II, open-label study

(LONESTAR-2) evaluated treatment with sofosbuvir, peginterferon, and ribavirin for 12 weeks; 50% of patients were cirrhotic. SVR occurred in 83% (10/12) of non-cirrhotics and 83% (10/12) of cirrhotics.[13] This regimen is not FDA approved.

VI. Identifying Treatment Candidates Based on Liver Disease Stage

HCV is a slowly progressive disease, usually requiring more than 20-40 years to progress to cirrhosis, but it may progress sooner in some patients, particularly among those who drink alcohol regularly. In non-cirrhotic patients, the short-term risk of developing a liver-related complication is low. Once a patient develops advanced cirrhosis, there is a higher likelihood of developing decompensated cirrhosis, including HCC, although the actual risk remains modest (<5% per year). Achieving SVR among patients with compensated cirrhosis reduces the risk of developing decompensated cirrhosis or HCC.

Patients with decompensated cirrhosis (Child-Turcotte-Pugh Class B or C; CTP score ≥7) have increased mortality, with median survival of 24 months or less. However, treatment options are limited for patients with decompensated cirrhosis. Treatment risks with interferon include infection and worsening hepatic function. The safety and efficacy data for sofosbuvir-based regimens among patients with decompensated cirrhosis are lacking. Since peginterferon is not recommended and no dosage recommendation can be given for simeprevir (if its use in combination with sofosbuvir were considered) in patients with decompensated cirrhosis, at the present time, the decision to treat and treatment follow-up of patients with decompensated cirrhosis should be made by an experienced and knowledgeable specialist.

Table 13. Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates

Method	Comment
Clinical Findings	• Physical exam findings (palpable left lobe, splenomegaly, palmar erythema) AND • Low platelet count (<100,000/mm^3)* AND • Abdominal imaging findings (see below)
Abdominal Imaging • Ultrasound • Computed tomography (CT) • Magnetic resonance imaging (MRI)	• Surface abnormalities (e.g., nodularity, and left lobe/caudate lobe hypertrophy) are suggestive of cirrhosis. • Features of portal hypertension (e.g., splenomegaly, recanalization of umbilical vein, collaterals) and ascites also are suggestive of cirrhosis.
Liver Fibrosis Imaging • Vibration-controlled transient elastography (Fibroscan®) • Acoustic radiation force impulse imaging (ARFI)	• Both elastography and ARFI are FDA-approved, ultrasound-based techniques for estimating the extent of liver fibrosis. • Fibroscan value of >12.5 kilopascals has been associated with histologic cirrhosis. • ARFI value of >1.75 meters/second has been associated with histologic cirrhosis.
Serum Markers of Fibrosis/Cirrhosis • APRI	• APRI and FIB-4 scores are easily calculated using standard clinical labs. • APRI >1.5 has been associated with advanced fibrosis (METAVIR F3);

Method	Comment
• FIB-4 • HALT-C cirrhosis score • Fibrosure, Fibrotest, Fibrospect	APRI >2.0 has been associated with cirrhosis (METAVIR F4) in the setting of chronic HCV infection. • FIB-4 >3.25 has been associated with advanced fibrosis (METAVIR F3-F4) in the setting of chronic HCV infection. • HALT-C cirrhosis score predicts likelihood of having cirrhosis based on standard clinical data. • Fibrosure, Fibrotest, and Fibrospect are proprietary, costly serum fibrosis assays that are not recommended for routine use in the diagnosis of cirrhosis.
Liver Biopsy	• Liver biopsy may be considered, but it is invasive and limited by potential sampling error. • METAVIR or Batts-Ludwig stage 4 fibrosis (on a scale from 0 to 4) or Ishak stage 5 or 6 fibrosis (on a scale from 0 to 6) confirms the diagnosis of cirrhosis.

Abbreviations: APRI = [(AST/upper limit of normal AST) x 100]/platelet count (10^9/L); FIB-4 = [Age (years) x AST]/platelet count (10^9/L) x $ALT^{1/2}$; HALT-C cirrhosis score (see www.haltctrial.org/cirrhosis.html)

* A low platelet count in the context of chronic HCV infection is predictive of histologic cirrhosis.

Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates (see Table 13): Noninvasive and invasive methods to determine the presence and stage of cirrhosis are continually evolving. Cirrhosis determination can be made using a histologic assessment of liver biopsy tissue. However, several limitations exist, namely, not all facilities offer this procedure, the quality of tissue is dependent upon the equipment and skill of the proceduralist; it is invasive, expensive, prone to sampling error and variability in histopathologic interpretation; and it carries a small risk of complications to the patient.

Serum markers: Routine blood tests can assist in identifying patients with advanced liver disease and, in some instances, predict the likelihood of developing decompensated disease or HCC. Serum markers of fibrosis (e.g., APRI, FIB-4, Fibrosure) may suggest the presence of advanced fibrosis or cirrhosis (Table 13). Similarly, the Ghany HALT-C score (www.haltctrial.org/cirrhosis.html) uses standard clinical data to predict the likelihood of a patient having cirrhosis. A score of >0.6 (i.e., >60%) is generally considered as an indication of cirrhosis. A Lok HALT-C HCC score greater than 3.25 (www.haltctrial.org/hccform.html) is associated with increased risk of developing hepatocellular carcinoma in the subsequent 3-5 years.

Platelet counts are an additional noninvasive tool to identify cirrhotic patients with more advanced cirrhosis. In the absence of hematopoietic disorders, patients with platelet counts of <150,000/mm^3 have increased risk of developing HCC, whereas patients with platelet counts of <100,000/mm^3 have an even higher risk of developing HCC.

Imaging: Findings of nodular liver or splenomegaly (>13 cm) on imaging (e.g., ultrasound, CT scan or MRI) suggest cirrhosis. Recently, the FDA approved two specialized ultrasound-based evaluations, vibration-controlled transient elastography and acoustic radiation force impulse imaging, to monitor liver fibrosis

progression. These modalities have been correlated with stage of histologic fibrosis; cutoffs that correspond to histologic cirrhosis have been developed, but may vary by population studied.

Hepatocellular carcinoma: The following is based on expert opinion, given that minimal data are available. Achieving an SVR is likely to improve outcome among patients in whom treatment is expected to remove/ablate the entire tumor (i.e., "curative intent") (e.g., transplant, surgical resection, and, potentially, radiofrequency ablation or TACE of small HCC). Thus, sofosbuvir/ribavirin treatment (possibly in combination with peginterferon) in these patients is reasonable, particularly for those awaiting liver transplantation and for those with a CTP score <7, given the available clinical trial data in this population and FDA labeling. Among patients in whom HCC treatment is noncurative (i.e., palliative), treatment of HCV is unlikely to provide significant prolongation of life or improvement in symptoms, and is not recommended until evidence of survival benefit is available.

VII. Laboratory Monitoring

Table 14. Discontinuing HCV Treatment Based on Lack of Virologic Response

Treatment Monitoring Considerations
• Patients receiving a sofosbuvir-based regimen should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is ≥25 IU/mL at Week 4 or at any timepoint thereafter, all treatment should be discontinued. (A-III) • Patients receiving a simeprevir-based regimen should have HCV RNA levels assessed at Weeks 4, 12 and 24; if the HCV RNA is ≥25 IU/mL at any of these time points, all treatment should be discontinued. (A-I)

Periodic laboratory monitoring of hemoglobin, hematocrit, white blood cell count with differential, platelet count, and liver enzymes is necessary in all patients receiving HCV antiviral therapy. Consider checking laboratory tests every 2 weeks initially for the first month, and then at least monthly thereafter, depending upon patient tolerability. HCV RNA levels should be assessed at 12 weeks after the end-of-treatment to determine if SVR was achieved. HCV RNA at 24 weeks after the end-of-treatment is suggested but optional. For further guidance on laboratory monitoring, refer to the *2012 Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office* (www.hepatitis.va.gov/provider/guidelines/2012HCV-supplement.asp, Supplemental Table 1).

VIII. Adverse Effects

Sofosbuvir[21]

The most common adverse events with sofosbuvir in combination with peginterferon and ribavirin were fatigue (59%), headache (36%), nausea (34%) and insomnia (25%). Approximately 10% of patients treated with sofosbuvir and ribavirin experienced a hemoglobin level of <10 g/dL and <1% developed a hemoglobin level of <8.5 g/dL. Neutropenia (absolute neutrophil count [ANC] <750/mm^3) and thrombocytopenia (platelet counts of <50,000/mm^3) were not observed. In studies with peginterferon, ribavirin, and sofosbuvir, 20% of patients developed a hemoglobin level of <10 g/dL and 2% developed a hemoglobin level of <8.5 g/dL. Neutropenia developed in approximately 20% of cases and

thrombocytopenia in <1% of cases. Anemia was managed by ribavirin dosage reduction in all studies, and <1% of patients received a blood transfusion.

Simeprevir[22]

The most common adverse effects of simeprevir, peginterferon and ribavirin regimens were rash including photosensitivity (28%), pruritus (22%), nausea (22%), dyspnea (12%), and hyperbilirubinemia (49%).

Rash and Photosensitivity

Rash including photosensitivity occurred most frequently in the first 4 weeks of treatment with a simeprevir, peginterferon, and ribavirin regimen, but can occur at any time during treatment. The majority (99%, 215/218) of rash and photosensitivity events were of mild (Grade 1) or moderate (Grade 2) severity. There were no reports of life-threatening (Grade 4) rash. Two simeprevir-treated patients experienced photosensitivity reactions that resulted in hospitalization. Rash and photosensitivity reactions were more likely to occur in patients with higher simeprevir exposures.

Patients should be counseled to use sun-protective measures, limit sun exposure, and avoid tanning devices during treatment with a simeprevir-based regimen. Patients with mild or moderate rash should be followed for possible progression of rash, including the development of mucosal signs (e.g., oral lesions, conjunctivitis) or systemic symptoms. If the rash becomes severe, simeprevir should be discontinued. Consider urgent medical care and dermatological consultation if needed. Patients should be monitored until the rash has resolved.

Dyspnea

In clinical trials of simeprevir, peginterferon, and ribavirin, increased dyspnea occurred in patients treated with simeprevir-based therapy compared with placebo-treated patients (12% and 8%, respectively); the majority of events occurred in the first 4 weeks of treatment. The dyspnea events were of mild or moderate severity (Grade 1 or 2). No patients discontinued simeprevir treatment due to dyspnea.

Hyperbilirubinemia

Approximately 50% of simeprevir-treated patients experienced elevated bilirubin levels compared with 26% of patients treated with placebo. Elevations of both direct and indirect bilirubin were predominately mild (Grade 1; >1.1 to ≤ 1.5 x ULN) to moderate (Grade 2; >1.5 to ≤2.5 x ULN) in severity. Bilirubin elevations occurred early after treatment initiation, peaking by week 2, and were rapidly reversible upon simeprevir discontinuation. Bilirubin elevations generally were not associated with elevations in liver transaminases.

Sulfa Allergy

Simeprevir contains a sulfonamide moiety. Based on limited data, patients with a history of sulfa allergy (n=16) did not appear to have an increased incidence of rash or photosensitivity reactions.

IX. Proper Use

Drug-Drug Interactions[21,22]

Sofosbuvir is not metabolized by the cytochrome P450 (CYP) system of enzymes but is a substrate of P-glycoprotein (P-gp); P-gp inducers may decrease sofosbuvir plasma concentrations.

- Sofosbuvir should not be coadministered with any of the following: St. John's wort, anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazepine), antimycobacterials (e.g., rifabutin, rifampin, rifapentine), or tipranavir/ritonavir.
- No dosage adjustment is needed for concomitant administration with the following: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, raltegravir, rilpivirine, tacrolimus, or tenofovir.

Simeprevir is metabolized by the CYP enzyme, CYP3A; coadministration with moderate or strong inducers or inhibitors of CYP3A is not recommended as this may decrease or increase simeprevir concentrations, respectively. Simeprevir is an inhibitor of P-gp and the drug transporter OATP1B1/3.

- Simeprevir should not be coadministered with any of the following: milk thistle, St. John's wort, HIV protease inhibitors (with or without ritonavir), efavirenz, etravirine, nevirapine, antiretroviral agents containing cobicistat, antimycobacterials (rifabutin, rifampin, rifapentine), macrolides, azole antifungals, ketolides, dexamethasone, anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazepine).
- No dosage adjustment is needed for concomitant administration with the following: cyclosporine, tacrolimus, ethinyl estradiol, norethindrone, methadone, omeprazole, rilpivirine, raltegravir, or tenofovir.

Refer to full prescribing information for a complete list of potential drug-drug interactions and dosage adjustments of concomitantly prescribed medications.

Sofosbuvir package insert: www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf
Simeprevir package insert: www.olysio.com/shared/product/olysio/prescribing-information.pdf

Storage and Stability[21,22]

Sofosbuvir and simeprevir tablets can be stored at room temperature (<86˚F), but exposure of the medication to direct sunlight should be avoided.

Humidity can alter sofosbuvir stability. Sofosbuvir was stable for 45 days in an open petri dish at 77°F with 60-75% relative humidity.

Missed Doses[21,22]

Patients should be instructed to take a missed sofosbuvir dose as soon as possible that day and to take the next sofosbuvir dose at the regular time the following day.

Patients should be instructed to take a missed simeprevir dose if it is less than 12 hours from the next scheduled simeprevir dose and to take the next simeprevir dose at the regular time the following day.

X. Groups with Special Considerations for Therapy

Table 15. HIV/HCV Coinfection, Genotypes 1 and 4: Preferred Regimens and SVR Rates from Supporting Data

Regimens with optimal efficacy, favorable tolerability and toxicity profile, and ease of use.

Treatment Considerations						Supporting Information	
HCV Genotype (GT) and Treatment Status	**Interferon Eligibility**	**Cirrhosis Status**	**Regimen and Duration**		**Evidence Grade**	**SVR% (N/N)**	**Comments**
GT1 or GT4, Treatment naïve or treatment experienced	Eligible	Non-cirrhotic or Cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-II/III	90% (18/20) in treatment-naïve, non-cirrhotics[a]	Single-center, single-arm, open label study
GT1 or GT4, Treatment naïve	Ineligible or intolerant*	Non-cirrhotic	Sofosbuvir + RBV	24 weeks	B-I	76% (87/114) in GT1 treatment-naïve with 4%, cirrhotics[b] Stratified by GT: GT1a: 82% (74/90) GT1b: 54% (13/24) (represents non-cirrhotic and cirrhotic patients)[b]	Reasonable to defer for future treatment if no significant extrahepatic disease, especially in GT1b-infected patients. The largest clinical trial to date of sofosbuvir/ ribavirin therapy was conducted in 114 patients with HIV/HCV coinfection. Among GT1b-infected patients with HIV/HCV co-infection, SVR was achieved in 54% (13/24) as compared with 82% (74/90) with GT1a infection.[b] **Consult with an ID/HIV specialist on treatment options.**
		Cirrhotic	*For consideration:* Sofosbuvir+ Simeprevir ± RBV	12 weeks	B-III	Data not available	**Treatment options are limited. The risk versus benefits of treatment must be carefully considered**

Treatment Considerations						Supporting Information	
HCV Genotype (GT) and Treatment Status	**Interferon Eligibility**	**Cirrhosis Status**	**Regimen and Duration**		**Evidence Grade**	**SVR% (N/N)**	**Comments**
			NOT FDA approved				**treatment must be carefully considered along with drug-drug interactions.** **Consult with an ID/HIV specialist on treatment options.** **The FDA does not address the use of simeprevir in HIV/HCV-coinfected patients.** **DO NOT USE sofosbuvir + ribavirin in cirrhotics due to insufficient data.**
GT1 or GT4, Treatment experienced	Ineligible or intolerant*	Non-cirrhotic or Cirrhotic	*For consideration:* Sofosbuvir+ Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-III	Data not available	**Treatment options are limited. The risk versus benefits of treatment must be carefully considered.** **Consult with an ID/HIV specialist on treatment options.** **The FDA does not address the use of simeprevir in HIV/HCV-coinfected patients.** **DO NOT USE sofosbuvir + ribavirin in treatment-experienced patients due to insufficient data.**

[a] Rodriguez-Torres et al. [19], [b] PHOTON-1[9]; Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; Sofosbuvir 400 mg orally daily. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

***Interferon ineligible or intolerant criteria:** See Table 5.

For HCV genotype 2 or 3 treatment considerations in HIV/HCV coinfection, refer to Tables 9-12.

HIV/HCV coinfection

Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) and peginterferon for 12 weeks is FDA approved for chronic HCV genotype 1 or 4 infection in treatment-naïve and treatment-experienced patients with HIV/HCV coinfection. (See Table 15.)

Sofosbuvir combined with weight-based ribavirin is FDA-approved for treatment-naïve and treatment-experienced HCV GT2-infected patients for 12 weeks and in HCV GT3-infected patients for 24 weeks with HIV/HCV coinfection. (See Tables 9-12.)

The preferred treatment for chronic HCV in HIV/HCV-coinfected patients is sofosbuvir plus peginterferon/ribavirin for 12 weeks or sofosbuvir/ribavirin for 24 weeks, because of improved tolerance and diminished potential for drug-drug interactions.

While there are few data on the use of simeprevir in HIV/HCV-coinfected individuals, the use of sofobuvir plus simeprevir (+/– ribavirin) for 12 weeks can be considered in IFN ineligible or intolerant GT1-infected patients, particularly those who are HCV treatment experienced. However, attention to drug-drug interactions between HIV and HCV drugs is needed. This regimen is not FDA approved.

The open-label Phase III clinical trial, PHOTON-1, examined the safety and efficacy of 12 and 24 weeks of sofosbuvir and ribavirin in HIV/HCV-coinfected patients with HCV GT1 (treatment naïve), 2, and 3 infection (treatment naïve and experienced). The mean CD4 count of study participants was >500 cells/mm^3. For all genotypes, response rates observed in HIV/HCV-coinfected patients were similar to response rates observed in HCV-monoinfected patients (Tables 9-12, 15). SVR12 and SVR24 rates were similar. For treatment-naïve GT1-infected patients, SVR12 and 24 rates to sofosbuvir and ribavirin for 24 weeks were 76% (87/114) and 75% (86/114), respectively. There was no difference in the SVR12 and 24 rates in those with GT2 infection and those with GT3 infection. For treatment-naïve patients, SVR rates to sofosbuvir and ribavirin for 12 weeks were 88% (23/26) in GT2-infected patients, and 67% (28/42) in GT3-infected patients. For treatment-experienced patients, SVR rates to sofosbuvir and ribavirin for 24 weeks were 92% (22/24) in GT2-infected patients and 88% (15/17) in GT3-infected patients. When GT1-infected patients were stratified by subtype, SVR12 rates were noted to be 82% (74/90) in those with GT1a infection and 54% (13/24) in those with GT1b infection. Only 4% of GT1- and GT2-infected patients, and 14% of GT3-infected patients had documented cirrhosis.[9,18]

A Phase II, single-center, open-label, single-arm trial evaluated 23 treatment-naïve, non-cirrhotic, GT1-4 HCV/HIV coinfected patients who received sofosbuvir, peginterferon, and ribavirin (1,000 or 1,200 mg/day) for 12 weeks. Patients were required to be on a stable HIV antiretroviral regimen with suppressed HIV RNA. Overall SVR was achieved in 91% (21/23). SVR occurred in 89% (17/19) of GT1-, 100% (1/1) of GT2-, 100% (2/2) of GT3-, and 100% of GT4-infected patients.[19]

Simeprevir use in HIV/HCV-coinfected individuals is not addressed in the FDA labeling. In an open-label study of 106 patients, simeprevir for 12 weeks plus peginterferon/ribavirin for 24 or 48 weeks was evaluated in treatment-naïve or treatment-experienced GT1 patients with HIV/HCV coinfection. The

overall SVR12 rate was 79% in treatment-naïve patients, 87% in relapsers to peginterferon/ribavirin, 70% in partial responders, and 57% in null responders to peginterferon/ribavirin. Protease-inhibitor or efavirenz-based regimens were not permitted in this study. F3-F4 disease was present in 21% of patients and SVR rates in this population ranged from 64% to 80%.[20]

Treatment options are limited in treatment-experienced, interferon-ineligible or interferon-intolerant HIV/HCV-coinfected patients with cirrhosis, and the risk versus benefits of treatment must be carefully considered. Consult with an ID/HIV specialist on treatment options. In interferon-ineligible or interferon-intolerant GT1 HIV/HCV-coinfected individuals, sofobuvir plus simeprevir (+/– ribavirin) for 12 weeks can be considered, particularly in HCV treatment-experienced cirrhotic patients. Although this regimen has not been studied in HIV/HCV-coinfected individuals and is not FDA approved, preliminary data (SVR4) in HCV-monoinfected patients suggests this may be a reasonable treatment option in HIV/HCV-coinfected patients. Furthermore, there are insufficient data with sofosbuvir plus ribavirin in treatment-experienced and cirrhotic HIV/HCV-coinfected populations to be able to recommend this regimen. Thus, for HIV/HCV-coinfected patients who are interferon ineligible or intolerant and for whom urgent treatment is required, consultation with an ID/HIV/ID expert is strongly recommended and, if sofosbuvir plus simeprevir (+/– ribavirin) is considered, a complete and thorough evaluation of potential drug-drug interactions is required.

HIV/HCV Drug-Drug Interactions[21,22]

Sofosbuvir has no significant interactions with antiretroviral drugs recommended for the treatment of HIV, including emtricitabine, tenofovir, efavirenz, darunavir (+/– ritonavir), rilpivirine, and raltegravir. Sofosbuvir and tipranavir (+/– ritonavir) should not be coadministered as this may diminish the therapeutic effect of sofosbuvir. Increased rates of hyperbilirubinemia were observed when sofosbuvir was coadministered with HIV regimens containing atazanavir (see “Adverse Effects in HIV/HCV Coinfection,” below).

Simeprevir should not be coadministered with the following HIV medications: HIV protease inhibitors (+/– ritonavir), efavirenz, etravirine, nevirapine, or antiretroviral agents containing cobicistat.

Use of zidovudine and didanosine with ribavirin is not recommended.

Adverse Effects in HIV/HCV Coinfection[21]

The most commonly reported adverse effects in HIV/HCV-coinfected patients treated with sofosbuvir and ribavirin were fatigue (30-38%), headache (24-30%), nausea (13-22%), and insomnia (15-16%). Hyper-bilirubinemia (total bilirubin >2.5 mg/dL) was observed in 22/114 (20%) of HIV/HCV patients treated with sofosbuvir and ribavirin for 24 weeks. Of these patients, 20 (95%) also were prescribed atazanavir-containing regimens; 5 patients were switched from atazanavir to darunavir. Approximately 20% of HIV/HCV-coinfected patients developed a grade 2 anemia (hemoglobin level of <10 g/dL) but only 2% developed a grade 3 anemia (hemoglobin level of <8.5 g/dL). One-fourth of HIV/HCV-coinfected patients required ribavirin dosage-reduction for management of anemia. For additional information, refer to Sofosbuvir (NDA 204671). Presentation to: FDA Antiviral Drugs Advisory Committee; October 25, 2013.

Selecting Patients for Treatment

Patients should be managed in collaboration with an ID/HIV specialist. Patients with uncontrolled HIV infection and advanced immunosuppression should begin HIV antiretrovirals before considering therapy for HCV. Optimal candidates for HCV treatment are patients who are on a stable regimen for HIV (HIV viral load <50 copies/mL) for at least 8 weeks and have an absolute CD4 count of >200 cells/mm^3.

Laboratory Monitoring[21,22]

In addition to the laboratory tests performed for HCV-monoinfected patients receiving antiviral therapy, HIV RNA and CD4 counts should be measured at baseline and at routine intervals as recommended by the Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.[23]

Renal Insufficiency or Hepatic Impairment

Table 16. Modification of Drug Use in Patients with Renal Insufficiency or Hepatic Impairment

Treatment Considerations			
Condition	**Treatment**	**Comment**	**Grade**
Renal Insufficiency	Simeprevir	Has not been studied in HCV-infected patients with CrCl <30 mL/min. However, no dosage adjustment needed.	A-I
	Sofosbuvir	Should not be used if CrCl <30 mL/min or end-stage renal disease.	A-I
	Peginterferon alfa-2a	Dosage reduce to 135 mcg/week subcutaneously once weekly for CrCl <30 mL/min, including hemodialysis.	A-I
	Peginterferon alfa-2b	Dosage reduce by 25% for CrCl 30-50 ml/min and by 50% for CrCl <30 ml/min, including hemodialysis.	A-I
	Ribavirin	200 mg daily alternating with 400 mg daily for CrCl 30-50 mL/min and 200 mg daily for CrCl <30 mL/min, including hemodialysis.	A-I
Hepatic Impairment	Simeprevir	No dosage recommendation can be given for patients with moderate or severe hepatic impairment (Child-Turcotte-Pugh Class B or C; CTP score ≥7) due to higher simeprevir exposures, which have been associated with increased frequency of adverse reactions including rash and photosensitivity.	A-I
	Sofosbuvir	No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment (Child-Turcotte-Pugh Class A, B, or C). Safety and efficacy of sofosbuvir have not been established in patients with decompensated cirrhosis.	A-I
	Peginterferon	Should not be used in patients with moderate or severe hepatic impairment (Child-Turcotte-Pugh Class B or C; CTP score ≥7).	A-I

CTP = Child-Turcotte-Pugh

Sofosbuvir[21]
Sofosbuvir and its major metabolites are eliminated primarily via renal clearance. No dosage adjustment is required for patients with mild or moderate renal impairment (CrCl ≥30 mL/min). However, the safety and efficacy of sofosbuvir are not established in patients with severe renal impairment (CrCl <30 mL/min). Hemodialysis removes 18% of the dose. Until additional data are available, sofosbuvir should not be used in patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease requiring dialysis.

Because peginterferon is not recommended and no dosage recommendation can be given for simeprevir in patients with decompensated cirrhosis (Child-Turcotte-Pugh Class B or C; CTP score ≥7), the safety and efficacy of sofosbuvir in combination with these agents have not been established. Collaboration with an experienced hepatologist is necessary to carefully consider the risks versus benefits of sofosbuvir-based treatment in patients with decompensated cirrhosis.

Simeprevir[22]
Simeprevir does not require dosage adjustment for mild, moderate, or severe renal impairment. No clinically significant differences in pharmacokinetics were observed in HCV-noninfected volunteers with mild, moderate, or severe renal impairment. Creatinine clearance was not identified as a significant covariate of simeprevir population pharmacokinetics in HCV-infected patients.

Simeprevir does not require dosage adjustment in patients with mild hepatic impairment (Child-Turcotte-Pugh Class A). In HCV-uninfected patients, the mean steady-state AUC of simeprevir was 2.4-fold higher with moderate hepatic impairment (Child-Turcotte-Pugh Class B) and 5.2-fold higher with severe hepatic impairment (Child-Turcotte-Pugh Class C). The safety and efficacy of simeprevir have not been established in HCV-infected patients with Child-Turcotte-Pugh Class B or C. Due to higher simeprevir exposure and potentially increased adverse reactions, no dosage recommendation can be given for simeprevir in patients with moderate or severe hepatic impairment (Child-Turcotte-Pugh Class B or C).

Treatment in Pre-Liver Transplant and Post-Liver or -Other Solid Organ Transplant

Table 17. Treatment Considerations for Patients Who Will or Have Received a Solid Organ Transplant, AFTER DISCUSSION WITH THE TRANSPLANT CENTER

Treatment Considerations					Supporting Information	
Transplant status	**HCV genotype (GT)**	**Regimen and duration**		**Evidence grade**	**SVR % (N/N)**	**Comments**
Pre-Liver Transplant for Patients with HCC	GT1, 2, 3, or 4	Sofosbuvir + RBV (combination with PEG-IFN may be considered	24-48 weeks	B-II	64% (25/39)[a]	Close collaboration with the transplant center is necessary prior to and during treatment. Patients had HCC with compensated liver disease (CTP score <7).

Treatment Considerations					Supporting Information	
Transplant status	**HCV genotype (GT)**	**Regimen and duration**		**Evidence grade**	**SVR % (N/N)**	**Comments**
		but is not FDA approved)				
Post-Liver Transplant	GT1, 2, 3, or 4	Sofosbuvir + RBV (PEG-IFN may be considered) **NOT FDA APPROVED**	24 weeks	B-III	77% (31/40)[b] 60% (19/32)[c] 50% (6/12)[c] with PEG-IFN	Close collaboration with the transplant center is necessary prior to and during treatment. Among patients with severe post-transplant HCV, 34% (15/44) mortality due to progressive liver disease and were not related to sofosbuvir/ribavirin therapy.
Post-Other Solid Organ Transplant (Kidney, Heart, or Lung)	GT1, 2, 3, or 4	Discuss with transplant center. **DO NOT USE (peg)interferon-containing regimens in these populations. Sofosbuvir has not been studied in non-liver transplant recipients.**				

CTP = Child-Turcotte-Pugh

[a] Curry MP et al. [24]; [b] Charlton MR et al. [25]; [c] Forns X et al. [26]

PEG-IFN = Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV = Ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; Sofosbuvir 400 mg orally daily. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75 kg and 1,200 mg/day if ≥75 kg, in divided doses) is FDA approved for HCV-infected patients with hepatocellular carcinoma meeting Milan criteria who are awaiting *liver transplantation, for a duration of up to 48 weeks or until the time of transplantation, whichever occurs first. (See Table 17.)*

Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (e.g., treatment once patient is listed for transplant). Sofosbuvir plus ribavirin treatment shows promise with evidence that the longer duration of viral negativity (i.e., >30 days) prior to transplant, the less likely virologic recurrence will occur. Among 61 patients with HCC awaiting liver transplant (median MELD of 8, CTP score <7) treated for up to 48 weeks, 41 had undetectable HCV RNA at the time of transplant.[24] In the 39 evaluable post-transplant patients, the 12-week post-transplant virologic response (pTVR) was 64% (25/39). The longest duration for which this regimen has been studied is 48 weeks, thus the timing of treatment initiation should be carefully considered.

Sofosbuvir and simeprevir are currently not approved by the FDA for use in post-transplant patients. (See Table 17.)

Sofosbuvir plus ribavirin has been evaluated in two Phase II trials of post-transplant HCV. Charlton and colleagues treated 40 patients with post-transplant HCV with sofosbuvir and ribavirin for 24 weeks. The majority of subjects were HCV GT1-infected (73%); 40% had cirrhosis and 23% had bridging fibrosis. In this study, the SVR rate was 77%. There were no deaths, graft loss, or rejection.[25] In a compassionate use program, Forns and colleagues treated 44 patients with severe recurrence of HCV following liver transplantation, including fibrosing cholestatic hepatitis, with sofosbuvir plus ribavirin either with (n=12) or without (n=32) peginterferon for 24 weeks. The decision to use peginterferon was left to the treating physician. The reported SVR was 60% for sofosbuvir and ribavirin and 50% for sofosbuvir, peginterferon plus ribavirin. Because of the severity of the HCV disease in the patients at the time of treatment initiation, 15 patients died of progressive liver disease during the treatment period. No deaths were attributed to sofosbuvir and ribavirin treatment. Liver function tests (e.g., bilirubin, INR) improved with treatment.[25] Although these trials were small, they are consistent in suggesting that sofosbuvir plus ribavirin may be safe and effective treatment for post-transplant HCV. Larger studies are needed to better evaluate safety and efficacy.

Sofosbuvir has not been studied in non-liver transplant settings. Close collaboration with the patient's transplant center is encouraged to assess post-transplant treatment candidate selection and type of regimen. Patients without urgent need for therapy would likely benefit from receiving future therapies that are more evidence-based.

Extra-hepatic manifestations of HCV

Table 18. Treatment of Patients with Extra-Hepatic HCV

Treatment Considerations
• Patients with leukocytoclastic vasculitis, symptomatic cryoglobulinemia or membranoproliferative glomerulonephritis despite mild liver disease should be treated as soon as possible.(A-III)

Mental Health and Substance-Use Disorders

Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. The use of interferon-containing regimens is associated with worsening of these conditions. Patients should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.

Substance or alcohol use: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT C (www.hepatitis.va.gov/provider/tools/audit-c.asp) or CAGE (www.hepatitis.va.gov/products/video-alcohol-brief-counseling.asp). The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. There are no published data supporting a minimum length of

abstinence as an inclusion criterion for HCV antiviral treatment. Patients with active substance- or alcohol-use disorders should be considered for therapy on a case-by-case basis and care should be coordinated with substance-use treatment specialists.

East Asian Ancestry[21]

Higher simeprevir exposure occurred among individuals of East Asian ancestry and has been associated with increased adverse reactions, including rash and photosensitivity.

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References

1. Martinot-Peignoux M, Stern C, Maylin S, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology. 2010;51:1122–26.

2. Medrano J, Barreiro P, Resino S, et al. Rate and timing of hepatitis C virus relapse after a successful course of pegylated interferon plus ribavirin in HIV-infected and HIV-uninfected patients. Clin Infect Dis 2009;49:1397-1401.

3. Chen J, Florian J, Carter W, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013;144:1450-55.

4. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878-87.

5. Jacobson IM, Dore GJ, Foster GR, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naive patients: efficacy in difficult-to-treat patient sub-populations in the QUEST 1 and 2 phase III trials. In: Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. Abstract 1122.

6. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir (TMC435) with peg-interferon α-2a/ribavirin for treatment of chronic HCV genotype 1 infection in patients who relapsed after previous interferon-based therapy: efficacy and safety in patient sub-populations in the PROMISE phase III trial. In: Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. Abstract 1092.

7. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014 Feb;146(2):430-41.e6.

8. Jacobson IM, Ghalib RH, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. In: Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. Abstract 1379.

9. Sulkowski MS, Rodriguez-Torres M, Lalezari JP, et al. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotype 1, 2, and 3 infection in patients co-infected with HIV (PHOTON-1). In: Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. Abstract 212.

10. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013 Aug 28;310(8):804-11.

11. Lalezari LP, Nelson DR, Hyland RH, et al. Once daily sofosbuvir plus ribavirin for 12 and 24 weeks in treatment-naive patients with HCV infection: the QUANTUM study. In: Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; April 24-28, 2013; Amsterdam, Netherlands. Abstract 845.

12. Gane EJ, Stedman CA, Hyland RH, et al. All-oral sofosbuvir-based 12-week regimens for the treatment of chronic HCV infection: the ELECTRON study. In: Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; April 24-28, 2013; Amsterdam, Netherlands. Abstract 14.

13. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir in combination with pegIFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment experienced patients with and without compensated cirrhosis: results from the LONESTAR-2 study. In: Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. Abstract LB4.

14. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74.

15. Zeuzem S, Dusheiko GM, Salupere R. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial. In: Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. Abstract 1085.

16. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013 May 16;368(20):1867-77.

17. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. The Lancet Infectious Diseases. 2013 May;13(5):401-8.

18. Naggie S, Sulkowski MS, Lalezari J, et al. Sofosbuvir Plus Ribavirin for HCV Genotype 1-3 Infection in HIV Coinfected Patients (PHOTON-1). In: Program and abstracts of the 21st Conference on Retroviruses and Opportunistic Infections (CROI 2014); March 3-6, 2014; Boston. Abstract 26.

19. Rodriguez-Torres M, Rodriguez-Orengo J, Gaggar A, et al. Sofosbuvir and Peginterferon alfa-2a/Ribavirin forTreatment-Naïve Genotype 1-4 HCV Infected Patients who are HIV Coinfected with HIV. ID Week 2013; October 2-6, 2013; San Francisco. Abstract 714.

20. Dieterich D, Rockstroh JK, Orkin C, et al. et al. Simeprevir (TMC435) plus PegIFN/ribavirin in HCV genotype-1/HIV-1 coinfection (Study C212). In: Program and abstracts of the 21st Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston. Abstract 24.

21. Sofosbuvir (SOVALDI™) [Package insert]. Gilead Sciences; Foster City, CA. 2013. Available at www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf. Accessed March 27, 2014.

22. Simeprevir (OLYSIO™) [Package insert.] Janssen Therapeutics; Titusville NJ. Available at www.olysio.com/shared/product/olysio/prescribing-information.pdf. Accessed March 27, 2014.

23. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed March 27, 2014.

24. Curry MP, Forns X, Chung RT, et al. Pretransplant sofosbuvir and ribavirin to prevent recurrence of HCV infection after liver transplantation. Hepatology. 2013; 58(Suppl.): 314A-5A.

25. Charlton MR, Gane EJ, Manns MP, et al. Sofosbuvir and ribavirin for the treatment of established recurrent hepatitis C infection after liver transplantation: preliminary results of a prospective multicenter study. Hepatology. 2013; 58(Suppl.): Abstr. LB-2.

26. Forns X, Fontana RJ, Moonka D, et al. Initial evaluation of the sofosbuvir compassionate use program for patients with severe recurrent HCV following liver transplantation. Hepatology. 2013; 58(Suppl.): 732A-3A.

The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection

A Technology Assessment

Final Report

April 15, 2014

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DATE OF PUBLICATION: April 15, 2014

Executive Summary

This assessment for the California Technology Assessment Forum (CTAF) evaluates the evidence on the comparative clinical effectiveness and value of two drugs recently approved by the FDA for the treatment of chronic hepatitis C: simeprevir and sofosbuvir. Chronic hepatitis C is a common infection that is a major cause of chronic liver disease, liver failure, and hepatocellular carcinoma, and it is the leading indication for liver transplantation in the Western world.[1] Prior to 2011, the combination of pegylated interferon and ribavirin (PR) was the gold standard of therapy for the treatment of chronic hepatitis C. Approximately half of patients with genotype 1, the most prevalent type of hepatitis C in the US, could expect with PR therapy to clear the virus from their bloodstream entirely and maintain a sustained virologic response (SVR) 24 weeks after the end of treatment. PR therapy can be difficult, however, as both interferon and ribavirin can produce bothersome side effects, and in some cases, dangerous levels of anemia, neutropenia, and/or thrombocytopenia.[2] The 2011 introduction of first generation direct-acting antiviral (DAA) protease inhibitors boceprevir (Victrelis®, Merck & Co.) and telaprevir (Incivek®, Vertex Pharmaceuticals, Inc.) resulted in substantially improved SVR rates in many patients when used with PR regimens. This improvement has come with new challenges, however, including significant additional side effects and drug-drug interactions as well as stringent dosing requirements and high pill burdens for patients.[3]

Novel DAA agents have been developed with the potential for simplified dosing, fewer side effects and drug-drug interactions, and in some patients, the promise of interferon- and/or ribavirin-free treatment, particularly for genotypes 2 and 3 (the other common genotypes in the US). These new agents include the recently-approved second generation protease inhibitor simeprevir (Olysio®, Janssen Products, LP) and polymerase inhibitor sofosbuvir (Sovaldi™, Gilead Sciences, Inc.), as well as several other agents that are currently in late-stage clinical trials. Uncertainties remain with these new agents, however, as data on treatment-related side effects and their performance in particular patient populations are still emerging in the published literature. In addition, the costs of treatment are likely to increase substantially, with the two new agents expected to cost approximately $70,000 and $170,000 per course of therapy, depending on the duration of therapy.[4,5] Accordingly, the California Technology Assessment Forum has chosen to review the evidence on the comparative clinical effectiveness and comparative value of new DAA agents for chronic hepatitis C in relation to the existing standard of care in multiple patient populations.

This assessment will address the following questions: 1) among patients with genotype 1, are treatment regimens incorporating simeprevir and sofosbuvir equivalent or superior to the previous standard of care: pegylated interferon plus ribavirin and one of the first generation protease inhibitors telaprevir or boceprevir; 2) among patients with genotypes 2 and 3, is the combination of sofosbuvir and ribavirin equivalent or superior to the previous standard of care, pegylated

interferon plus ribavirin; and 3) among interferon-ineligible or intolerant patients, is the combination of sofosbuvir plus ribavirin or sofosbuvir plus simeprevir equivalent or superior to no treatment. The purpose of this assessment is to help patients, providers, and payers address these important questions and to support dialogue needed for successful action to improve the quality and value of health care for patients with hepatitis C.

Methods

The lack of head-to-head trials makes it difficult to assess the relative efficacy of the different drug regimens. In order to assess the relative efficacy of various treatment options, we performed a network meta-analysis, a form of indirect comparison that synthesizes direct and indirect evidence in a network of clinical trials to compare multiple interventions for the same indication. Network meta-analysis allows for indirect comparisons between therapies as long as they have the same type of control group (often placebo) in randomized trials.

To examine the potential clinical and economic impact of the introduction of sofosbuvir and simeprevir in California, we also developed a cohort model that assessed these effects over time horizons of one year, five years, and 20 years. Our model examined outcomes in different hypothetical cohorts of chronic hepatitis C patients organized by genotype, prior treatment status (i.e., treatment-naïve versus treatment-experienced), and eligibility for interferon therapy. Within each of these strata, outcomes and costs were assessed for a cohort of 1,000 hypothetical patients, age 60 years. We focused on genotypes 1, 2, and 3, as these represent over 97% of the hepatitis C population in the US.

Results

Genotype 1

Table ES1 on the next page summarizes the key benefits and harms for the treatment options for genotype 1. Among treatment-naïve patients, the first generation protease inhibitors increase the SVR at 12 weeks (SVR12) from the 40% range with PR to the 70% range. However, a large number of pills have to be taken about every 8 hours, and there are burdensome new side effects. These include a marked increase in anemia, with nearly 50% of patients taking telaprevir requiring erythropoietin stimulating agents for a median of 15 weeks during the course of treatment. Also common were nausea for both boceprevir and telaprevir, 20% more patients experiencing taste disturbance for boceprevir, and 20% more patients experiencing generalized pruritus with telaprevir. The drugs also have a large number of important drug interactions. Despite these problems, triple therapy with one of the two first generation protease inhibitors and PR was considered the standard of care for treatment of genotype 1 until the approval of simeprevir and sofosbuvir.