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December 8, 2015

Jerry Menikoff, M.D., J.D.
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Re: Federal Policy for the Protection of Human Subjects, Federal Register Vol. 80, No. 173, September 8, 2015

Dear Dr. Menikoff,

The Council on Governmental Relations (COGR) is an association of 190 research universities and their affiliated academic medical centers that conduct over \$60 billion in research and development annually. As principal performers of human subjects research, much of it conducted in partnership with federal agencies, our members have a vested interest in the proposed changes to the regulations governing this research.

We would like to begin by saying that we appreciate the intent of the proposed rule to strengthen, modernize and make more effective the regulations protecting human subjects, and to decrease administrative burden, delay and ambiguity. Efforts made in good faith to reduce burden without reducing protections, such as the elimination of continuing review for minimal risk research are meaningful and appreciated. Where member institutions believe that proposed revisions will reduce administrative burden without compromising the protection of human subjects we support them in this letter. As an example, with a few caveats, we also support the expansion of exempt research and the promise of additional categories that will qualify for expedited review.

Conversely, there are major proposed revisions that would lead to a significant increase in burden, delay, ambiguity, and cost, and a loss of valuable research without increasing protections for human subjects. These include expanding the definition of a "human subject" to include biospecimens; the proposed requirements for consent for all biospecimens regardless of identifiability and restrictions on the use of consent waivers; mandatory use of Health Insurance Portability and Accountability Act (HIPAA) or alternative, but yet-to-be determined, data security provisions; mandatory reliance on a single Institutional Review Board (IRB) for multi-site studies; and the inclusion of non-regulated, unfunded trials under the regulations for the subset of organizations which receive federal grants.

Of significant concern is what we perceive to be a lack of balance among the ethical principles articulated in the Belmont Report. In particular, we are concerned that the proposed treatment of biospecimens inappropriately emphasizes the principle of respect for persons (autonomy), with seemingly little regard for beneficence and justice. We are dismayed to see controversial policies proposed or implemented by the National Institutes of Health (NIH) dominate this proposed rule despite strong opposition from many who provided well-reasoned feedback during the Advanced Notice of Proposed Rulemaking (ANPRM) comment period and in response to proposed NIH policy. With this Notice of Proposed Rulemaking (NPRM), the Department of Health and Human Services (HHS), by seeking to impose mandates rather than developing practicable policies in cooperation with the research community, fails to recognize the partnership that exists between the federal government and the research institutions and principal investigators who carry out federally-assisted research.

In addition to a significant imbalance among the ethical principles articulated in the Belmont Report, there is a significant imbalance with respect to the benefits and costs of a number of provisions. In a similar respect, some provisions geared toward reducing investigators' administrative burden merely shift additional burden to institutions.

We are very concerned that this NPRM (with 88+ questions and proposed alternative regulations) reads like an Advanced Notice and may result in a final rule that, depending on the tools developed, options chosen, and direction taken, has the potential to substantially increase the cost and administrative burden of implementing the Common Rule revisions with little benefit for the protection of human subjects. With respect to the proposed informed consent template, security standards, list of expedited-eligible procedures, and decision tool for identifying exempt research, we cannot adequately comment on how useful they might be, since they are not yet developed. Also, we doubt that they can be fully developed and appropriately tested in the implementation timeframes cited when these concepts have not been advanced in the four intervening years since the release of the ANPRM.

We recommend that those elements of the NPRM that are undeveloped (i.e., the decision tool; consent template; Secretary's safeguards; and Secretary's list of minimal risk research) be removed from the proposed rule and developed independently. The HHS Office for Human Research Protections (OHRP) should work collaboratively with representatives from the research community and research funding agencies to develop these areas. We do not believe it is appropriate to include them even in an interim final rule, as this would not allow for additional substantive changes and would start the clock on implementation.

HHS should publish beneficial, consensus items as a final rule. These include elimination of continuing review (without additional notification requirements) for minimal risk studies that qualify for expedited review; identification of the types of research that are excluded from the regulations with an indication that the list is not all inclusive; development of proper and clear guidance on these types of exclusions for investigators; adding a new provision that would explicitly give Common Rule departments and agencies the authority and obligation to enforce compliance directly against unaffiliated IRBs that are not operated by an assured institution; updating and expanding the Secretary's list of research eligible for expedited review -- we suggest that any research deemed to be no more than minimal risk by a reviewer be considered eligible for expedited review; and the elimination of the requirement that the IRB review grant applications for congruency with IRB applications. We believe these revisions would

reduce administrative work for investigators and institutions without reducing human subjects protections.

We strongly urge OHRP to eliminate from the proposed regulations the highly controversial proposals related to biospecimens, cooperative research, and expanding coverage to non-federally funded clinical research. In drafting these proposed changes we believe HHS has failed to appreciate the complexity of the issues, the potential negative impact on research, and the overwhelming cost and burden that would result from implementing them. For example, we believe that the majority of institutions will not have the resources to comply with the proposed changes specific to biospecimens. Non-identified biospecimens collected in a non-research setting during the course of clinical care are likely to be discarded or sent to entities that are not subject to the regulations. Research involving biospecimens will be significantly impeded and billions of dollars will be reallocated from research to compliance without adding to the protection of human subjects.

While we believe that the NPRM is not well developed enough to allow for appropriate review and comments, we are providing COGR's observations on major topic areas described in the NPRM. We also include detailed responses to the questions included in the NPRM in the addendum to this letter.

Biospecimens and Expanding the Definition of Human Subject

COGR strongly opposes the proposal to expand the definition of a "human subject" to cover research with non-identified biospecimens as proposed at .102(e)(1) and to require informed consent for research involving biospecimens in all but a limited number of circumstances. We believe non-identifiable biospecimens should remain excluded from the regulations and not subject to consent. There is a very low risk of harm arising from research conducted with these specimens. Conversely, if the definition is changed and the proposed provisions are put into place, we believe that countless specimens will become unusable, and research that is of significant value to society will not be conducted, resulting in significant harm.

The inclusion of biospecimens as a "special" or "protected" class of material is problematic for many reasons. First and foremost, biospecimens, in and of themselves, are not "human subjects." Second, from a security perspective, we are not aware of any instances in which researchers have violated confidentiality or other non-disclosure agreements in order to re-identify individuals' de-identified specimens that resulted in any harm or loss of privacy for the subjects involved. Risk to donors is addressed by removing identifiers and through the use of institutions' security safeguards and can be further mitigated by prohibiting unauthorized re-identification and imposing sanctions if it were to occur. Critical research should not be stifled due to the availability of public genetic genealogy or related databases. Legislation that addresses unauthorized re-identification and greater effort to educate the public about the risks and scientific value of genetic studies involving secondary use of biospecimens (e.g., development of innovative diagnostics, treatments, cures or preventative interventions) would more effectively balance privacy and autonomy concerns with the need for valuable biospecimen research than re-categorizing this research as human subjects research.

As noted earlier, we believe there is a substantial imbalance between the Belmont principles that would have a significant negative impact on research involving biospecimens to the detriment of society at large. Broad consent for future use of biospecimens would greatly expand consent practices, particularly in non-research settings, and would require documentation and tracking. This is where the

proposed benefits have to be balanced with what we believe will be significant direct financial costs, an increased need for human resources, and a direct decrease in the number and types of biospecimens available for a wide variety of uses.

The basis repeatedly cited for the proposal to require consent for all biospecimen research (even research with non-identified biospecimens) is that this is what specimen donors reportedly want. Four studies are cited and all appear to presume that institutions collecting specimens will always have the needed resources to ask every individual for research consent, and to track that consent, which simply is not the case. Only the largest, wealthiest research hospitals may be able to afford the required infrastructure and one would expect such infrastructure costs to be charged as a direct cost to grants, further reducing research funding. In the studies cited, subjects were asked whether they would prefer opt-in, opt-out or no consent, but were never asked whether they would rather have their residual specimen discarded rather than used in research if seeking consent is not an option. In fact, most studies report that subjects think biospecimen research is critical and that the vast majority of specimen donors would consent to use of their biological tissues. We believe that the results of the studies upon which the proposed regulations are based would likely have been different if the options had been explained in light of the impact on medical advances; participants might have agreed that no consent was preferable to the destruction of biospecimens, the disproportionate loss of specimens from underrepresented groups, and the resulting decline in life-saving research – especially as related to non-identified specimens.

General Consent and Waiver of Consent

A summary of the ANPRM findings presented to the HHS Secretary's Advisory Committee for Human Research Protections (SACHRP) by an OHRP staff member in February 2012¹ suggests that the majority of responses were favorable to use of a standardized, general consent form to permit future research on biospecimens and data (question 49 of the ANPRM), but also that the wording of the question appeared to be unclear, with some responding to the concept of requiring a standard consent and others supporting the notion of having a standard form available for use, as desired. Findings from an analysis of a random sample (300) of the 1100+ comments DHHS received in response to the ANPRM included in the article "Public Comments on Proposed Regulatory Reforms That Would Impact Biospecimen Research" published in the September/October 2015 issue of IRB Ethics and Human Research², suggest the majority opposed mandated consent. In this analysis, the authors focused on those comments specific to biospecimens (109), including mandated written consent, waiver of consent, and the inherent identifiability of biospecimens. In terms of support for mandated consent, they found that 9 supported it, 9 indicated qualified support, and 69 did not support mandated consent. Asked whether specimens should be considered inherently identifiable, 15 indicated yes and 44 no.

Regarding support for waiver of consent (Q. 67), 70 supported waiver, 8 indicated qualified support, and 3 did not support the use of waivers. We also note that in the summary of ANPRM comments presented to SACHRP, a "very strong majority" favored allowing waiver of consent for the collection and study of existing data and biospecimens provided they are non-identified and met existing waiver

¹ Bartlett, EE. February 2012. ANPRM: Summary of Comments. Retrieved from: <http://www.hhs.gov/ohrp/sachrp/mtgins/2012%20Feb%20Mtg/anprmsummaryebartlett.pdf>

² Cadigan, RJ, Nelson, DK, Henderson, GE, et al. September-October 2015. Public Comments on Proposed Regulatory Reforms That Would Impact Biospecimen Research: The Good, the Bad, and the Puzzling. IRB Ethics and Human Research; 37(5). Retrieved from: <http://www.thehastingscenter.org/Publications/IRB/Detail.aspx?id=7554>

criteria. Given the support for waiver of consent, we question why the NPRM proposes to make such waivers “rare.” We suggest that each research project should be viewed independently based on the merits of the scientific knowledge to be gained, weighed against respect for individuals’ rights to consent. IRBs have successfully managed this decision point for some time and have both the experience and ability to interpret the current waiver criteria within their ethical frameworks that allows important research to continue while protecting human subjects. No evidence is presented that this approach has compromised privacy for human subjects. If consent were sought in conjunction with a specific protocol, irrespective of how broad the consent might be, this should not trigger a prohibition on waiving consent for secondary research of biospecimens and identifiable information. This proposed change will reduce flexibility for the IRB and investigator and increase burden without increasing human subjects protections.

With respect to the three additional proposed elements of consent specific to biospecimens (i.e., commercial use and profit, disclosure of results, and the option to refuse re-contact), we feel that this does not represent broad consent and that it further emphasizes autonomy over beneficence and justice and therefore oppose these measures. We also ask why research with biospecimens is again being treated differently from other types of research.

Consent for Non-identified Biospecimens Collected in a Non-research Setting

The proposed rules, including the requirement for broad consent, are of even greater concern regarding the use of excess non-identified materials collected for purposes other than research and again we strongly oppose the proposed changes. Institutions partner with large health systems, community hospitals and clinics which provide non-identified specimens but whose primary mission is not research. At the time of collection, whether and how these specimens will be used in research cannot be predicted. Since these specimens are not collected for a specific research project, there will be no IRB protocol with an investigator at hand to obtain consent. Instead, hospitals and clinics would have to train nurses, staff and phlebotomists to obtain such consent, document the results and have a system in place to maintain the documentation for the time when an investigator with a protocol requires access. With large health systems, the numerous entry points for patients would require development of complex information management systems to track broad consent and withdrawal of consent processes. Private laboratories and physician practices would need to be included in these systems. We believe that hospitals and clinics will not have the resources to implement the proposed changes, nor is it part of their mission. Therefore, they are unlikely to develop the costly infrastructure required to obtain and track research consent for clinical specimens. The expansion of the definition of human subjects research to include such non-identified specimens would therefore be devastating to the progress of new diagnostics, therapeutics and individualized cures for disease in the future.

The potential costs of this new rule are impossible to quantify. It is not just the high cost of infrastructure and administrative/research time that must be weighed, rather it is the loss of new knowledge and potentially the loss of lives that could have otherwise been saved through biospecimen research. In addition, due to the high entry cost required to build the sophisticated technical capacity necessary to implement these new rules, we believe biospecimens from underserved populations will be subject to the greatest decline, resulting in data-sets that are less heterogeneous and further reducing adherence to the principles of justice and beneficence. Millions of samples are collected each year, only

a fraction of which are used. Predicting their use is impossible, as is consenting for use in all settings, and these samples are likely to be discarded if this rule is enacted.

We note that per an ANPRM summary of comments presented to SACHRP by an OHRP staff member in February 2012, a “strong majority” of those commenting on the ANPRM was opposed to changing the current practice of allowing research on biospecimens that have been collected outside of a research study (i.e., leftover tissue following surgery) without consent, as long as the subject’s identity is never disclosed to the investigator. We strongly support the position put forth in the National Academy of Sciences’ 2015 report, *Optimizing the Nation’s Investment in Academic Research: A New Regulatory Framework for the 21st Century: Part 1*. The report endorses the current standard that non-identifiable biospecimens collected for purposes other than research should continue to be excluded from coverage under the Common Rule. We agree with the Committee’s findings that “requiring consent for all research involving biospecimens would substantially increase administrative burdens on investigators, research staff and institutions” and “markedly hinder the conduct of critical science” and suggest that it would not increase human subjects protections.

Alternative Proposals

We strongly believe that the current definition of “human subject” and practices regarding biospecimens should not be altered, and question why OHRP has chosen to ignore the majority of stakeholder comments in response to the ANPRM. Regarding the three definitions offered (questions 4 and 5), Alternative Proposal A, expanding the definition of “human subject” to include only specifically whole genome sequencing data or parts of data, would appear to be the most reasonable of the three options. It would have a far less negative impact on research given that “relatively little whole genome sequence research” is taking place (the NPRM estimates 300 current studies). The NPRM notes that, in 2012, the Presidential Commission for the Study of Bioethical Issues recommended that “unauthorized whole genome sequencing without the consent of the individual from whom the sample came” be prohibited.³ Perhaps most relevant is the recommendation that “researchers and clinicians should evaluate and adopt robust and workable consent processes that allow research participants, patients, and others to understand who has access to their whole genome sequences and other data generated in the course of research, clinical, or commercial sequencing, and to know how these data might be used in the future.”

Regarding Alternative A, we suggest that the definition of human subject need not be changed to render this information subject to the Common Rule. The current definition of human subject includes “identifiable private information” and private information is described as information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information). The NPRM notes that “recent developments have made it possible to use whole genome sequencing information to re-identify non-identified data.” To the extent that whole genome sequencing information may result in identifiable information, it may be reasonable to suggest that these data, and the samples used to generate them, meet the standard of “identifiable” (if not “readily”) rendering them subject to the Common Rule without a change to the definition of human subject. The report also recommends that “accessible whole genome sequence data should be stripped of traditional identifiers whenever possible to inhibit recognition or re-

³ Retrieved from: http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf

identification.” This is better accomplished by not expanding the definition of human subject and requiring the creation of a recorded and traceable consent record for secondary research use. Identifiable whole genome sequence data, the reports notes, is already covered under HIPAA.

Regarding consent for secondary research use of whole genome data, this option would significantly reduce the need to obtain and track consent for secondary use, rendering the costs more manageable. Broad consent for whole genome sequencing with an opportunity to opt-out is, in this situation, an appropriate compromise between respect for the individual to make a decision about whether their specimen should be used in research, and the ability to use that specimen in the broadest and most beneficial way for society at large. Participants would be informed about potential risks for research that is most likely to yield identifiable results, therefore more appropriately tailoring regulation to risk and respect for persons. In this case, inclusion in the general healthcare consent of the broad research consent language which the agency plans to develop should be sufficient for future research use. Institutions should have the ability to modify broad consent language as necessary to address a range of future uses and populations.

Alternative Proposal B is not appropriate, as it proposes to define a human subject based on analytical technologies rather than on individuals. Given that the use of a technology, in and of itself, does not render materials identifiable, this is not an appropriate standard. While a technology may have the capability of generating information unique to an individual, the rule should not apply unless generating that information is a specified purpose of the research as in the case of whole genome sequencing. The modifier “may be readily ascertained” in the definition of private identifiable information within the definition of human subject is useful, as it allows for changes in scientific technology and data sharing over time and for assessments to be made in real time.

Alternative C, which is the treatment of biospecimens as currently written in the NPRM, is wholly inappropriate. The summary at the beginning states that, “the NPRM seeks to avoid requirements that do not enhance protection and impose burden, which can decrease efficiency, waste resources, erode trust, and obscure the true ethical challenges that require careful deliberation and stakeholder input. Cumbersome and outdated regulatory standards overwhelm and distract institutions, IRBs, and investigators in ways that stymie efforts to appropriately address the real risks and benefits of research.” This proposed treatment of biospecimens embodies burden, a decrease in efficiency, wastes significant resources, and will overwhelm institutions, IRBs, and investigators. This alternative comes at a significant cost to research, our understanding of disease, and the development of new therapeutics without improving protections. By requiring consent for all specimens, irrespective of the original purpose of the specimen collection, (and by caveat, removing specimens from biorepositories if an individual wished to later revoke consent for use), it establishes a requirement to maintain linkages to identifiers for all biospecimens even if there is no reason to do so other than to document informed consent. This, in and of itself, creates greater vulnerability for identification than the genetic materials contained within samples. Further, it requires the development of costly and extensive data security systems when they would otherwise be unnecessary.

Guidance for Biospecimens

As we have stated, we believe the special status given non-identified biospecimens is inappropriate. If, against the strong recommendations of the research community, the agency continues to treat

biospecimens as innately identifiable and deserving of special protections, we strongly urge HHS to address the issues of concern through guidance that is thoroughly vetted by the research community at a later time.

Regulatory Impact

There is a significant imbalance with respect to the benefits and costs of requiring broad consent for secondary use of biospecimens. The NPRM suggests that quantified costs for obtaining consent to secondary use of biospecimens and identifiable private information are \$12.245 billion of the projected total cost of \$13.342 billion for implementing the proposed revisions. It indicates that the cost “to obtain, document and track the permissible uses of biospecimens and identifiable private information for secondary research use is not quantified.” We believe these costs will be the most significant of all of the proposed revisions and that overall the costs, while staggering, represent a substantial underestimate. In response to the proposed revisions to the Common Rule specific to biospecimens, the American Society for Investigative Pathology suggests that “the NPRM has underestimated the financial impact of the Common Rule changes by a factor of at least ten.”⁴ We believe many universities will not have the resources to implement tracking systems for consent. Where tracking is implemented, the increase in costs will necessarily result in direct charges to those grants and contracts using the data and specimens. The end result of this proposed change (in addition to a reduction in the number of samples available for research use) is that billions of dollars would no longer be available for conducting research.

While the intended goal of increasing autonomy is laudable, the considerable cost and potential loss of research and capacity to benefit the public at large renders this a completely unrealistic approach. The proposed changes will not increase human subjects protections, nor will they reduce burden. On the contrary, the proposed changes would reduce protections by increasing identifiability; run counter to the principles of justice and beneficence by significantly reducing community-based samples in favor of biospecimens collected from only the wealthiest university-affiliated hospitals and institutions; impede or prevent research that could lead to new discoveries and cures; and dramatically increase the administrative workload of investigators and university administrators as well as technology and infrastructure costs. Further, the economic and human impact of the loss of biospecimens and reduction in secondary use are not assessed.

The NPRM suggests that it is anticipated that these revisions will result in higher value research with biospecimens being conducted with subjects’ consent and without the need to go back to subjects to obtain consent for every secondary research study, as long as certain conditions are met. It is not clear how this will increase value and the suggestion that this will reduce burden is unsound.

Cooperative Research

COGR believes that use of single IRBs for multisite studies can be an effective and efficient mechanism to initiate multicenter protocols in appropriate situations. However, we do not support mandated use and strongly urge OHRP to abandon such a mandate as a component of the Common Rule. Expanding use of a single IRB for multisite studies can be addressed outside of regulations at an agency’s discretion (as demonstrated by the NIH), is currently operationally under-developed by agencies, will

⁴ Retrieved from: <http://www.asip.org/SciencePolicy/documents/ASIPCommentsNPRMCommonRule.pdf>

not improve human subject protections, and is destined to create a bureaucratic quagmire for investigators and institutions. This provision will not “streamline or reduce burden for IRBs or institutions” as proposed on page 53996 of the NPRM.

We urge HHS to address institutional liability issues and to partner with agencies with an interest in expanding use of single IRB (NIH, in particular) and the research community to assess models which will be successful without the need for a regulatory “stick” to drive the process. If single IRBs are mandated, there will be little incentive for current problems in the system to be resolved because agencies will fall back on the Common Rule requirements and leave institutions to struggle. For the single IRB system to succeed, agencies such as NIH need to better refine their current attempts. We also urge OHRP to define cooperative research such that social and behavioral collaborations do not fall under its aegis and the number of engaged institutions is far greater than two.

As suggested, COGR’s member institutions support the concept of relying on a single IRB where appropriate and this practice is increasingly adopted. We do not support a mandate for the following reasons:

An Absence of Data on Cost, Efficiency and Protections

There is a lack of data demonstrating that relying on a single IRB, as it is proposed in the NPRM and NIH draft policy, is more efficient and cost effective and that such a requirement will not diminish human subjects protections. Experience suggests that there is not a reduction in burden, that additional administrative work is shifted to institutions and that the timeline for review is not shortened. We believe the suggested cost benefits in the RIA related to cooperative research are in error and that no cost benefit will be realized. On the contrary, we believe there will be significant additional costs for the sites serving as the single IRB and little to no savings for relying sites. It is inappropriate to mandate such a comprehensive model that has not been developed and shown to be feasible within the current federal funding and operating constraints.

Reliance Agreements, Ancillary Reviews and State and Local Concerns

There are significant costs and timelines associated with establishing reliance agreements between collaborating research sites and maintaining required documentation at the reviewing IRB.⁵ Resolving issues of liability and indemnification and documentation requirements between institutions also adds time and effort to the review process that may result in significant delays. To address this, the NPRM proposes a compliance date three years from the publication of the final rule. In the unfortunate event that HHS imposes such a mandate this delay will be welcome, but such a delay will not alleviate this concern as new agreements will be generated for most studies. It is not a matter of setting up one (or a few) agreement(s) over a period of time that institutions will then consistently use. Hundreds of agreements will be developed on an ongoing basis. The high degree of variability by having multiple organizations, public and private, with a mosaic of state laws, and institutional policies, practices, technologies, and cultures, serving as central IRBs creates a problem which cannot be fixed by model agreements. One key to success is using a limited number of central IRBs. For example, if each institute at the NIH had its own central IRB in the National Cancer Institute (NCI) model, this could be viable.

⁵ Retrieved from: <http://www.sciencemag.org/content/350/6261/632.short>

In addition to negotiation and execution of agreements and standard operating procedures, study initiation meetings, account activity set-up, and modification of IT systems there are ancillary review processes e.g., COI, biosafety and radiation safety, which must still occur at each local institution and state specific requirements that may necessitate additional local review and site-specific changes to informed consent.

Many institutional IRBs are also not appropriately staffed or equipped to administratively support the review of a study involving a significant number of sites. Central review is likely to disproportionately fall to institutions with large research programs which likewise may not be appropriately staffed to support these studies. Any institution which will be required to serve as a central IRB will require additional resources in order to accomplish this, and to date a source for these resources has not been identified.

A Single IRB Is Not Appropriate for All Studies (Q. 76)

We also note that single IRBs are not appropriate for all multisite research. For example, use of a single IRB should not be extended beyond studies where there is an identical protocol implemented at all sites. Single IRB would not be the best model for studies that are designed for collaboration across several institutions with each institution having a discrete role based on local expertise or resources.

Single IRB is also most appropriate when there is a plan to run several protocols through the same IRB. If the single IRB model is not coupled with multiple projects, it will not save time. We also note that applying such a policy to studies with two or more sites would be inefficient. For the purposes of such a policy, 30 or more sites might be more appropriate, though evidence-based criteria should be used in making this determination. Finally, social and behavioral science is not better served by a single IRB review. The genesis of this model is in medical clinical trials and should be restricted primarily to these types of studies, not to minimal risk research.

Responses to the ANPRM and NIH Proposed Policy on Use of a Single IRB

These and other concerns are detailed in responses to the NIH Request for Comments on the Draft NIH Policy on the Use of a Single IRB for Multisite Research. We note that, like the responses to the Common Rule ANPRM, most comments in full support of the policy were not from those with experience implementing and using single IRBs. Those with detailed knowledge of the process expressed significant reservations with the current draft policy, suggesting that the policy is premature in its breadth; that essential details were omitted; and that the policy would potentially result in hundreds of different “single IRBs of record” with which institutions and investigators would have to interact – all with different rules of engagement. It was suggested that, given there is no current body of evidence indicating a precise path forward on which to base policy, mandating a single IRB of record as a solitary solution seems quite premature. Research institutions suggested that an initial policy should be piloted, narrowly focused, include appropriate resources, maintain flexibility, and that NIH should evaluate potential benefits and costs. Many suggested the creation of discipline-specific central IRBs (CIRB) at the federal level consistent with the NCI CIRB.

The NPRM suggests that SACHRP comments on the draft NIH policy⁶ were “generally supportive of voluntary increased use of a single IRB for multisite studies.” We note that in response to the draft NIH policy, SACHRP has suggested that mandating single IRB review for domestic multi-site studies is not the appropriate solution to improve turn-around time for human subjects research, that it is premature at this time to mandate single IRB use in NIH-funded domestic multi-center trials, and that requiring a single IRB to review a multi-site research protocol may result in new procedures and policies being created that will undermine the goals of the policy change and create a host of new challenges for research institutions. We strongly support all of the SACHRP recommendations including that NIH convene meetings with the research community where issues regarding the use of a single IRB can be discussed in a public forum.

How Should the Federal Government Encourage Expanded Use of Single IRB?

COGR supports the proposal to add a provision at .114(b)(1) that would explicitly give Common Rule departments and agencies the authority to enforce compliance directly against unaffiliated IRBs that are not operated by an assured institution. Clarifying the institutional liability issue would certainly facilitate a greater willingness to rely on another institution’s IRB. The NPRM noted that OHRP has previously proposed such a change which received widespread support, but it was never implemented for unexplained reasons. Furthermore, it is not clear why the issue of institutional liability needs to be embedded in regulation rather than guidance and practice by regulatory agencies such as OHRP.

There are two viable paths forward for accelerating the use of a single IRB for multi-site studies. The first would be establishing NIH institute-specific central IRBs for large multi-site studies which institutions fully endorse. The second would be working with the research community to evaluate existing models, forms and systems for use in institution-led single IRBs and to develop and pilot additional models as needed. These agreements should be voluntary, and both options will require a significant investment on the part of the federal government in outreach, time, and funding that has not existed to date.

Exemptions and Exclusions

Explicit Exclusion of Activities from the Common Rule

The NPRM creates a new section in the regulations referred to as “exclusions”, activities that will be outside the scope of the regulations. We observe that the activities that are *deemed not to be research* under the proposed rule are also deemed “not human subjects research” under the current regulations as they do not meet the definition either of “human subjects” or “research.” To the extent HHS moves forward with the exclusion category we believe the subcategories should be removed and the exclusions presented as illustrative examples, lest it become prescriptive in its interpretation. The OHRP overview webinar indicates that the categories are largely descriptive headings that don’t affect the conditions of the exclusions but auditors are unlikely to accept this interpretation. We agree that these activities should be excluded from the regulations (question 9) and make the following observations:

- We continue to maintain that non-identified biospecimens should be retained in the exclusion category.

⁶ Retrieved from: http://www.hhs.gov/ohrp/sachrp/commsec/useofasingle_irb.html

- The exclusion of Quality Assurance or Improvement activities should not be limited to those where the purpose is to alter the utilization of an accepted practice. Comparative assessment of alternative practices to determine relative effectiveness should continue to be excluded from the regulations. Quality improvement goals in healthcare facilities would otherwise be impeded and burden and cost greatly increased without a resultant increase in the protections afforded patients. These activities are primarily based on the principles of epidemiology and surveillance and are outside the scope of the Common Rule.
- Regarding “activities that are excluded because they are considered to be low risk,” we believe that the exclusion of research involving the collection or study of information which is either publically available or non-identifiable, will be helpful in eliminating a set of studies from IRB consideration. The fourth such exclusion, however, requires that an investigator receiving public health information (PHI) from a covered entity needs to be from a covered entity as well. This is an unnecessary stipulation as the HIPAA Privacy Rule already requires the IRB to determine that the recipient will protect the identifiers from improper use and disclosure, has an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, and has given adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, unless required by law or by oversight of the research by a regulatory agency.

There are no procedures offered for making an exclusion determination. Presumably, an investigator would make that determination with no assistance from the IRB. OHRP could consider developing a tool for investigators to determine what “excluded research” is. As currently written, some of the exclusions are sufficiently nuanced that many investigators might be confused about the meaning and lost in the nomenclature and Code of Federal Regulations (CFR) references. One approach would be to provide investigators with a robust decision tree in order to facilitate compliance with this element. In fact, one decision tree resulting in either an exclusion or exempt determination (or indicating that some form of review is needed) would help investigators to determine the correct category of research. The same provisos, however, would pertain to the use of any tool OHRP might develop, as detailed for exempt research, below.

Regarding question 16, since these categories are excluded from the regulation, we do not believe it is appropriate to impose regulatory requirements regarding documentation or record retention. To do so would be contrary to the concept of “excluded” and would inappropriately bind the institutions to verify such records are kept, adding unnecessary burden and cost.

Decision Tool

The Exempt Wizard, a tool for researchers to self-determine exempt status, was developed by faculty at a COGR institution in consultation with OHRP as a Federal Demonstration Partnership (FDP) project. Although we believe it has promise, the Wizard was not widely used and not extensively tested. It was also developed under the existing Common Rule, so any pilot data do not apply to its utility with the proposed, more complex and nuanced Rule. It is impossible for us to evaluate any proposed decision tool which has yet to be developed or validated. As noted in our introduction, we recommend that language and questions pertaining to the proposed tool be removed from the NPRM, that a tool be developed and tested in cooperation with the research community, and that a notice be republished separately once such a tool is developed.

In theory, we support the concept of a tool developed by the federal government which would serve the same purpose as the Wizard. Our qualified approval comes with several important provisos:

- 1) For simplicity and consistency, one tool should be agreed upon by all of the sponsoring agencies.
- 2) The agencies must involve research administration professionals in developing such a tool so that it has field-friendly workability.
- 3) The tool should be validated by institutions and investigators (the FDP would be a valuable partner in this undertaking).
- 4) The decisions produced by the tool will only be as good as the tool and the materials and guidance that accompany it. To the extent institutions are not engaged in the process, institutions should not be held accountable for any unintended outcomes. It is unlikely, however, that the use of a federal decision tool would shield the institution or investigator from liability in third party actions.
- 5) Clear indication that the tool determines exemption from federal regulations and state restrictions still apply.

We don't believe these criteria can be met in the timeframe proposed for completing the final rule. If, as proposed, investigators are going to make the exclusion determination without input from the IRB, it is essential for OHRP to develop very clear and concise guidance as well as educational materials. Such guidance should include information that is easy to understand and include examples.

Regarding audit of these decisions, we appreciated seeing the audit proposal removed from the NPRM, but were disappointed to see it included as a question which could allow for its reintroduction in the final rule. By the very nature of the low risk associated with exempt research, assigning resources to audit these studies will reduce attention to higher risk studies. We note that in a summary of ANPRM comments presented to SACHRP, a strong majority were opposed to the auditing requirement.

Proposed Exemptions

COGR supports the expansion of exempt research. We are also pleased to see that the exempt categories are applicable to the majority of the Subparts. However, as a basic principle, exempt research should mean that the category of activity is exempt from the regulation. The proposed exemptions should not be subject to documentation requirements, privacy safeguards, or limited IRB review. We believe that introducing privacy safeguards and other requirements confounds the notion of exemption. If the agency determines that a category of research requires review, documentation or other requirements such as notice, then this is no longer an "exempt" category of research and should be added to the Secretary's list of minimal risk research that qualifies for expedited review. Possible candidates might include surveys involving sensitive information or research involving the use of deception. This could also be established through the use of a decision tool if done correctly. It is essential for clarity to the research community that any requirements or obligations be consistent within categories of research.

Additional requirements notice – question 39 – also should not be imposed on this exempt research. Since the concept of a decision tool is that the results will not be reviewed by an IRB, if a notice were required, it must be a standard notice developed by agencies and available for use by investigators. Such a notice would need to carry the agency's "safe harbor" standard as being acceptable without modification if the rule is going to require its use.

The new exemption involving what is now called “benign interventions” should be renamed to better reflect its nature. The meaning of these two words commonly connote medical procedures, but are being used here to describe social and behavioral science studies. They are not benign in the sense that they are beneficial to the subject, but are rather, neutral in that they will not convey harm. They are also not “interventions” in the conventional sense, but rather, interactions with the investigator or computer to perform certain tasks. Similar to the privacy safeguards, above, this exemption adds another burden to the IRB review in that it requires the subject’s prospective agreement to the intervention and data collection. Again, we believe that if a study is “exempt” further requirements should not be attached. We also believe it would be helpful to include marketing studies in this category and that the list be framed as examples rather than being prescriptive.

We note that §_.109, IRB Review of Research, seems to suggest that an IRB would not be able to approve, require modifications in, or disapprove exempt research activities. Although the exemptions are written to assure that only minimal risk research is included, there are always exceptional circumstances in which an IRB might believe that for a particular project subjects could be at risk and might suggest modifications to the study or, in the absence of its ability to mitigate the risk, the IRB or institution could disapprove the research. Because IRBs’ primary mission is the protection of human subjects, their authority should not be diminished by these regulations. The proposed revision to §.109 (a), “that do not qualify for exemption pursuant to §.104(d),(e), or (f)(2)” should be deleted. We further note that at §_.112, Review by Institution, the authority is given to the institution to disapprove any research covered by the policy. In the event that this section could be interpreted as not including exempt research, we recommend that this language be revised to explicitly include it.

Privacy and Security Safeguards (Q. 43)

We note that in a summary of ANPRM comments presented to SACHRP in February 2012, a “strong majority” opposed the use of data security and information protection standards modeled on the HIPAA rules and to additional data security standards (for exempt research). IRBs currently evaluate data security in the context of the nature of the research and information collected and stored. Therefore, a wide range of options are available which are scaled appropriately under the approval of the IRB and security standards continue to be enhanced to effectively protect research information.

It is not possible to evaluate proposed safeguards because the agency security standards are not provided. We strongly recommend that the data security requirements for all data except those currently covered by HIPAA be removed from the NPRM until such time as the agency provides a complete proposal for alternative standards which can be appropriately reviewed by both the research and information technology (IT) communities and applied only when the data being secured warrants such protection.

The NPRM suggests that, once the safeguards list is developed and issued, it will be open to public comment, and that there will be flexibility regarding the application and implementation of the data security safeguards. We suggest that safeguards should be manifested as tiered levels of data security protection corresponding to the level of risk. In drafting the data security safeguards, the Secretary should consider the robust data security policies and procedures developed at institutions and allow for adherence to such policies. Defaulting to the decidedly less flexible HIPAA standards would be inappropriate for the wide range of research activities subject to the Common Rule. We note that the

HIPAA regulations do not cover de-identified specimens and conflict with the NPRM's proposed limits on the use and disclosure of identifiable data and biospecimens. The HIPAA standard should only be employed when protected health information is involved in the research. OHRP should clarify that HIPAA covered entities are not required to expand HIPAA to meet the .105 standard.

Changes to Promote Effectiveness and Efficiency in IRB Operations

Continuing Review of Research

COGR fully supports the proposed elimination of continuing review for minimal risk studies that qualify for expedited review as proposed in §.109(f). Additionally we support the elimination of continuing review for studies initially reviewed by a convened IRB, unless specifically mandated by the IRB, after the study reaches the stage where it involves one or both of the following: (1) analyzing data, or (2) accessing follow-up clinical data from procedures that subjects would undergo as part of standard of care for their medical condition or disease. The Flexibility Coalition has advocated for this change, and for those institutions that have implemented such a strategy, there have been only positive results evidenced through less work for researchers as well as for IRB staff. In most cases, the continuing review for minimal risk research imposes an administrative burden that does not result in the discovery of information or issues that require IRB or investigator action. In some cases, the requirement for continuing review results in noncompliance issues from lapses in IRB approval that do not represent risk to research participants. COGR acknowledges that exempt research described in §.104(f) requiring "limited IRB review" does not require continuing review.

We do not support the requirement for researchers to provide an annual certification. Although many institutions support the concept of tracking current active projects, we do not believe there is a need to regulate this check-in. Investigators are already obligated to notify the IRB of any changes to their studies. This is an example of where flexibility would be eliminated without improving protection for human subjects.

Expedited Review Procedures and the Definition of "Minimal Risk"

We support expedited review for studies on the Secretary's list unless the reviewer(s) determine(s) that the study involves more than minimal risk. The NPRM proposes that the list of expedited review categories be re-evaluated at least every 8 years. A summary of ANPRM findings presented to SACHRP suggests that periods ranging from annually to every 5 years were recommended with a mean of 2.9 years. The current list, published in 1998, has never been updated. We agree that regular review, at least every 8 years but optimally 5, makes sense.

Stakeholders should be engaged in the process of developing the amended list prior to publication in the Federal Register. Further, the expedited review process should not be limited to the research procedures described on the Secretary's list, but rather should be used for any research deemed to be no more than minimal risk by the IRB Chair or designee as suggested in the ANPRM. This would significantly reduce the administrative workload of investigators and institutions without reducing human subject protections and the frequency with which the list was updated would be of less concern.

We would also like to suggest that if the exempt categories in §.104(f) (data/specimen repositories and secondary use) require use of the expedited review procedure to determine that a project meets

regulatory approval criteria at §_111(a)(9), then conceptually it would be more appropriate to include them on the expedited list rather than defining this as exempt research.

Required Elements of Informed Consent

We support the notion that consent forms first provide essential information that a reasonable person would want to know in order to make an informed decision and that any additional information should be placed in the appendix. We would suggest that the current length is due to the level of detail that has historically been required by regulatory agencies and see nothing in the NPRM that will alter this. We would support moving risks of standard care to the appendix. Evidence-based guidance on form language and the entire consent process would be more beneficial than regulating the format of consent forms.

Documentation of Informed Consent

We do not see the utility of the proposed provision to publish consent forms to a public website as it creates a new administrative burden without providing any clear additional protection for research subjects or benefit to the public at large (contrary to what is suggested in the NPRM). The executive summary of the NPRM indicates the provision would assure that the proposed rules on informed consent “change current practices” and the NPRM overview webinar, that people writing consent forms will “think about doing a better job” if they know the forms will be posted online. We don’t believe this would be an effective tool to ensure adherence to proposed rules on informed consent. Evidence-based guidance based upon an analysis of subject understanding would go further in improving the informed consent process. Also, due to timing issues, such posting could provide outdated, erroneous or misleading information to anyone reviewing the site. This proposed revision would succeed only in wasting resources (projected at 14.6 million dollars).

Other Proposed Changes

Extending the Common Rule to Include All Clinical Trials (Q. 85)

As we noted in response to the ANPRM, extending the Common Rule to all research, regardless of funding source, at an institution that receives federal funding for non-exempt and non-excluded human subject research (§_101(a)(1)) will not strengthen human subject protections as suggested in the NPRM. Domestic academic medical centers and institutions of higher education already review all human subject research through an IRB whether or not it is regulated by OHRP or the Food and Drug Administration (FDA). The box is unchecked not to apply a different ethical standard but to avoid those administrative burdens imposed in the current regulations that don’t impact the protection of human subjects, such as federal reporting requirements. The proposed regulation will have unintended consequences by increasing the administrative burden on the conduct of minimal risk behavioral and social science research that involve randomization without adding protections to the human subjects involved in these trials and will not impact the organizations that likely cause the greatest concern for the public including private hospitals, clinics, or other health-related entities that do not receive federal funds and conduct clinical trials.

What the proposed expansion would do is require a single IRB for all studies meeting the definition of a clinical trial regardless of the funding source, including minimal risk studies. It stems from the desire

for clinical trials to have single IRB review, but doesn't differentiate between medical and behavioral research and would now apply to behavioral and social sciences research as well. This will add significant burden to major research universities as they will likely be designated as the lead institution, but it will not serve to better protect subjects, as the local knowledge, so essential to many social and behavioral research studies, will be lost.

While the costs related to a multi-center trial may potentially be charged to the sponsor, many behavioral studies (e.g., student research, smoking cessation, eating disorders, and other behavioral modification programs) have no funding source and would have to be established and operated at a cost to the institutions. The proposed regulation will increase the administrative burden on both institutions and researchers, create delays in research, increase the costs of research, and potentially discourage some collaborative research. It removes institutions' ability to be flexible with how they apply the regulations without increasing human subject protections. We strongly oppose the proposed expansion. We also recommend that the definition of "clinical trial" should be limited to research studies of "greater than minimal risk" and not include "behavioral health-related outcomes."

Changes to the Assurance Process

COGR fully supports the elimination of the requirement that the IRB review grant applications for congruency with IRB applications. The IRB application is designed to cover all aspects of the human research for the funded award and must be updated whenever changes are proposed. It should have all the information the IRB needs for its review.

A proposed change at § .115 states that copies of all research proposals reviewed, scientific evaluations, etc. must be maintained. The commentary to the NPRM on page 53991 states that it is eliminating the requirement at 103(f) that grant applications undergo IRB review and approval for the purposes of certification. The language in .115 should make clear that the research proposals being referenced are not those submitted to a funding agency, but rather, those submitted to the IRB for review. "IRB-reviewed protocols" may be a better term for what the IRB needs to approve and maintain.

We welcome changes to streamline federal requirements, but do not agree that removing the "box" from the Federal wide Assurance (FWA) would be a mechanism to achieve this and believe this is simply a byproduct of the proposed revision to extend Common Rule coverage to all clinical trials regardless of funding source. OHRP should encourage institutions to explore flexibility through guidance and other directives on effective practices for reducing regulatory burden for low-risk research.

Harmonization of Agency Guidance (Q. 73)

The NPRM language on harmonization is weak and we feel very strongly that it would be completely ineffective in preventing duplication which significantly and unnecessarily increases administrative work. The proposed rule requires nothing other than an agency seeking "consultation." Even this "consultation" can be waived if an undefined "feasibility" standard is not met. This does not set any standard regarding inconsistency, duplication, or other problems research universities currently encounter. A much more formal process with third party (e.g., Office of Information and Regulatory Affairs) evaluation is needed.

We oppose the proposed revision allowing agencies discretion regarding additional requirements imposed by the conducting or supporting department or agency. This would not “promote harmonization” as suggested, but increase variance in the implementation of the Common Rule. Consistency in the implementation of any revisions to the Common Rule among the 17 Federal agencies signing on will be essential and harmonization with FDA regulations critical.

Regulatory Impact Analysis

The NPRM provides estimated costs and benefits of the proposed changes. A review of the tables indicates that the costs used for hourly wages of individuals affected by the proposed changes may be underestimated by as much as 12% - 139% (see Table 1). Similarly, the hours associated with the changes are substantially underestimated. In fact the NPRM itself states (pg. 53996, D. Analysis of Benefits and Costs) that; a) because of the lack of available data about IRB effectiveness and how IRBs function operationally, many of the estimations in this analysis are based on anecdotal evidence; b) many of the estimates are from a 1998 NIH sponsored evaluation (that is, approximately 17 years outdated). On the other hand it appears that the estimated benefits are significantly overestimated (e.g., cooperative research) to present a distorted view of the cost versus benefits. It should be added that the costs do not include any additional burdens that may be imposed by yet undescribed/undeveloped provisions of the proposed rules, e.g., the assessment tools. Due to the inadequacy of the cost benefit analysis in the NPRM, we request that this analysis be revaluated and republished for public comments prior to issuance of any final notice.

Table 1: Proposed salaries of IRB members and officials.

<u>Title/Role</u>	<u>Average Annual Salary</u>	<u>Hourly rate</u> (Based on 40 hour weeks, 52 weeks per year)	<u>NPRM Estimate</u>	<u>Difference</u>	<u>% Increase</u>	<u>Source</u>
Investigators						Science Magazine: 2013 Life Sciences Salary Survey
<i>Professor</i>	\$151,633	\$72.90	\$35.75	\$37.15	104%	
<i>Associate Professor</i>	\$108,428	\$52.13	\$35.75	\$16.38	46%	
<i>Assistant Professor</i>	\$83,635	\$40.21	\$35.75	\$4.46	12%	
IRB Voting Members						All but community members are faculty engaged in research with similar salaries
Institutional Officials						2013 Survey; Administrators in Higher Education Salary Survey, College and University Professional Association for Human Resources salaries Senior Research Officers at PhD granting institutions
	\$241,196	\$115.96	\$48.50	\$67.46	139%	
IRB Chair	\$151,633	\$72.90	\$46.36	\$26.54	57%	Generally a Senior Faculty member at Professor level
IRB Staff	\$67,086	\$32.25	\$16.72	\$15.53	93%	Glassdoor.com average salary for IRB analyst/coordinator

Even in the current estimation, HHS indicates that the cost to implement the proposed regulations is \$13.342 billion over a ten year period and the proposed benefits only \$2.629 billion (including highly questionable financial benefits associated with cooperative research) resulting in additional costs of over \$1 billion per year. Research universities would be subject to astronomical costs for policies that are not aimed at improving human subjects protections, but rather represent misguided means to reduce investigators' administrative workload and to foster the principle of autonomy while sacrificing the principles of beneficence and justice. An effective government-university partnership cannot exist when the federal government mandates unnecessary and costly regulations and policies that will significantly stress the capacity of universities to conduct federally funded research and in the face of universities' strong opposition to such policies. If the federal government truly believes that these policies are essential to the conduct of research, the federal government should develop and fund the necessary infrastructure to support them rather than proposing mandates that provide neither. We suggest that HHS and other participating agencies have not proposed regulatory approaches that maximize net benefits, in accordance with Executive Order 12866.

Conclusions

In closing, COGR strongly recommends that the current definition of "human subject" and practices regarding biospecimens not be altered. The proposed changes, including broad consent for storage and secondary research use of biospecimens regardless of identifiability, would result in a significant loss of research without improving protections for human subjects.

We do not support mandating a single IRB for all multi-site studies and strongly urge OHRP to abandon the single IRB concept as a component of the Common Rule. OHRP should address institutional liability issues through guidance and partner with agencies and the research community to assess the efficiency of existing models and evaluate new models as necessary. Expanding the use of the NCI CIRB and creating similar disease focused federal IRBs funded by NIH should be given serious consideration.

COGR does not support expanding the Common Rule to include all clinical trials which would serve only to mandate single IRB for non-federally funded trials. It would not improve human subject protections for these studies as all institutions subject to the Common Rule already extend this coverage, and it would extend coverage to social and behavioral studies that are of minimal risk and would not benefit from a single IRB.

COGR agrees that certain activities should be excluded from the Common Rule. We suggest this list should be presented as examples, lest it become prescriptive in its interpretation. Regarding the proposed decision tool, we recommend that it be removed from the proposed rule and developed independently. HHS should work with the research community to develop and pilot an effective tool.

COGR supports the expansion of exempt research. We recommend, however, that as a basic principle, exempt research should mean that the category of activity is in fact exempt from the regulation and not subject to additional requirements. If additional requirements are necessary, the activity should be added to the Secretary's list of minimal-risk research qualified for expedited review. This list should be developed in consultation with the research community and should not be considered all-inclusive. IRBs should have the ability to determine if research not included on the list meets the standards for minimal risk. COGR also fully supports the proposed elimination of continuing review for minimal risk

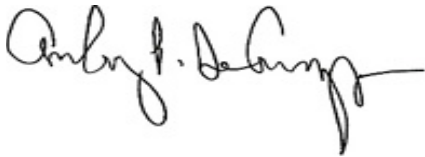
studies that qualify for expedited review and for studies initially reviewed by a convened IRB after the study reaches data analysis or clinical follow-up stages.

As noted in this letter, there are unresolved complexities throughout the NPRM. We recommend that those areas that are undeveloped (i.e., the decision tool; procedures for determining exclusions; consent template; Secretary's safeguards; and the Secretary's updated list of minimal risk research) be eliminated from a final rule. As a means to complete the rule in a timely and fair way while ensuring effective forms, tools and safeguards, OHRP should create working groups with representatives from the research community and research funding agencies to develop these tools.

Finally, we note that given considerable inadequacies in the cost benefit analysis included in the NPRM, this analysis should be reevaluated and republished for public comments prior to issuance of any final notice. We also recommend that greater consideration be given to the proposed costs of the regulations with the goal of creating an appropriate balance between benefits and costs.

We appreciate the opportunity to comment on this proposed rulemaking and look forward to continuing this dialogue as OHRP takes necessary steps toward completion of a final rule.

Sincerely,

A handwritten signature in black ink, appearing to read "Anthony DeCrappeo". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Anthony DeCrappeo

President, COGR

Addendum: Responses to Common Rule NPRM Questions

1. Public comment is sought on whether the proposed changes will achieve the objectives of (i) decreasing administrative burden, delay and ambiguity for investigators, institutions, and IRBs, and (ii) strengthening, modernizing, and making the regulations more effective in protecting research subjects.

Response: Overall, the proposed changes will not achieve the stated objectives. Selected components of the proposed rule changes will ease the burden on investigators and IRBs, in particular, the reduction in continuing reviews. Conversely, there are major proposed revisions that would lead to a significant increase in burden, delay, ambiguity, and cost, and a loss of valuable research without increasing protections for human subjects. These include expanding the definition of a “human subject” to include biospecimens; the proposed requirements for consent for all biospecimens regardless of identifiability and restrictions on the use of consent waivers; mandatory use of Health Insurance Portability and Accountability Act (HIPAA) or alternative, but yet-to-be determined, data security provisions; mandatory reliance on a single Institutional Review Board (IRB) for multi-site studies; and the inclusion of non-regulated, unfunded trials under the regulations for the subset of organizations which receive federal grants.

HHS should publish beneficial, consensus items as a final rule. These include elimination of continuing review (without additional notification requirements) for minimal risk studies that qualify for expedited review; identification of the types of research that are excluded from the regulations with an indication that the list is not all inclusive; development of proper and clear guidance on these types of exclusions for investigators; adding a new provision that would explicitly give Common Rule departments and agencies the authority and obligation to enforce compliance directly against unaffiliated IRBs that are not operated by an assured institution; updating and expanding the Secretary’s list of research eligible for expedited review -- we suggest that any research deemed to be no more than minimal risk by a reviewer be considered eligible for expedited review; and the elimination of the requirement that the IRB review grant applications for congruency with IRB applications. We believe these revisions would reduce administrative work for investigators and institutions without reducing human subjects protections.

We strongly urge OHRP to eliminate from the proposed regulations the highly controversial proposals related to biospecimens, cooperative research, and expanding coverage to non-federally funded clinical research. In drafting these proposals we believe HHS has failed to appreciate the complexity of the issues, the potential negative impact on research, and the overwhelming cost and burden that would result from implementing them. For example, we believe that the majority of institutions will not have the resources to comply with the proposed changes specific to biospecimens. Non-identified biospecimens collected during the course of clinical care are likely to be discarded or sent to entities that are not subject to the regulations. Research involving biospecimens will be significantly impeded and billions of dollars will be reallocated from research to compliance without adding to the protection of human subjects.

2. Would providing a definition of biospecimen be helpful in implementing this provision? If so, how might the definition draw a line between when a biospecimen is covered by the Common Rule, and when processing of biological materials (e.g., to create a commercial product used for treatment purposes) has sufficiently altered the materials so that they should not be subject to the regulations? Would only covering biospecimens that include nucleic acids draw an appropriate line?

Response: The inclusion of biospecimens as a “special” or “protected” class of material is problematic for many reasons. First and foremost, biospecimens, in and of themselves, are not “human subjects.” Second, from a security perspective, we are not aware of any instances in which researchers have violated confidentiality or other non-disclosure agreements in order to re-identify individuals’ de-identified specimens that resulted in any harm or loss of privacy for the subjects involved. Risk to donors is addressed by removing identifiers and through the use of institutions’ security safeguards and can be further mitigated by prohibiting unauthorized re-identification and imposing sanctions if it were to occur. Critical research should not be stifled due to the availability of public genetic genealogy or related databases. Legislation that addresses unauthorized re-identification and greater effort to educate the public about the risks and scientific value of genetic studies involving secondary use of biospecimens (e.g., development of innovative diagnostics, treatments, cures or preventative interventions) would more effectively balance privacy and autonomy concerns with the need for valuable biospecimen research than re-categorizing this research as human subjects research.

There is no need to draw a line between a biospecimen covered by the Common Rule and when processing for commercial purposes, as the latter does not constitute “research.” It is most important that all understand what constitutes “research,” and subsequent actions will flow from this determination. Only covering biospecimens that include nucleic acids would not address the fundamental issues of considering biospecimens as “human subjects.”

3. To what extent do the issues raised in this discussion suggest the need to be clearer and more direct about the definition of identifiable private information? How useful and appropriate is the current modifier “may be readily ascertained” in the context of modern genomic technology, widespread data sharing, and high speed computing? One alternative is to replace the term “identifiable private information” with the term used across the Federal Government: Personally identifiable information (PII). The Office of Management and Budget’s 45 concept of PII refers to information that can be used to distinguish or trace an individual’s identity (such as their name, social security number, biometric records, etc.) alone, or when combined with other personal or identifying information which is linked or linkable to a specific individual, such as date and place of birth, mother’s maiden name, etc. It is acknowledged that replacing “identifiable private information” with “PII” would increase the scope of what is subject to the Common Rule. However, the practical implications of such an expansion, other than the need to ensure that the data are securely stored and otherwise protected against disclosure, may be minimal. Public comment is requested on the advantages and disadvantages of such a change.

Response: The current definition is adequate and should not be replaced with personally identifiable information. We are not aware of any significant breaches which would have been averted in light of a new standard. Therefore, we strongly encourage continuing use of the current definition within the Common Rule.

The modifier “may be readily ascertained” in the definition of private identifiable information within the definition of human subject is useful, as it allows for changes in scientific technology and data sharing over time and for assessments to be made in real time. What was readily ascertainable 10 years ago has changed and will be different 10 years from now. This allows IRBs and researchers to assess identifiability based on current technology, data sharing and computing capabilities, as opposed to comparing it to a prescriptive or inclusive list of identifiers or scientific technologies provided by OHRP as part of the federal regulations.

4. Which of the three proposals regarding the definition of human subject achieves the most reasonable tradeoff between the principles of autonomy (including transparency and level of trust) versus beneficence (as measured by facilitating valuable research)?

Response: We strongly believe that the current definition of “human subject” and practices regarding biospecimens should not be altered, and question why OHRP has chosen to ignore the majority of stakeholder comments in response to the ANPRM. Regarding the three definitions offered, Alternative Proposal A, expanding the definition of “human subject” to include only specifically whole genome sequencing data or parts of data, would appear to be the most reasonable of the three options. It would have a far less negative impact on research given that “relatively little whole genome sequence research” is taking place (the NPRM estimates 300 current studies). The NPRM notes that, in 2012, the Presidential Commission for the Study of Bioethical Issues recommended that “unauthorized whole genome sequencing without the consent of the individual from whom the sample came” be prohibited.⁷ Perhaps most relevant is the recommendation that “researchers and clinicians should evaluate and adopt robust and workable consent processes that allow research participants, patients, and others to understand who has access to their whole genome sequences and other data generated in the course of research, clinical, or commercial sequencing, and to know how these data might be used in the future.”

Regarding Alternative A, we suggest that the definition of human subject need not be changed to render this information subject to the Common Rule. The current definition of human subject includes “identifiable private information” and private information is described as information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information). The NPRM notes that “recent developments have made it possible to use whole genome sequencing information to re-identify non-identified data.” To the extent that whole genome sequencing information may result in identifiable information, it may be reasonable to suggest that these data, and the samples used to generate them, meet the standard of “identifiable” (if not “readily”) rendering them subject to the Common Rule without a change to the definition of human subject. The report also recommends that “accessible whole genome sequence data should be stripped of traditional identifiers whenever possible to inhibit recognition or re-identification.” This is better accomplished by not expanding the definition of human subject and requiring the creation of a recorded and traceable consent record for secondary research use. Identifiable whole genome sequence data, the reports notes, is already covered under HIPAA.

Regarding consent for secondary use of whole genome data, this option would significantly reduce the need to obtain and track consent for secondary use, rendering the costs more manageable. Broad consent for whole genome sequencing with an opportunity to opt-out is, in this situation, an appropriate compromise between respect for the individual to make a decision about whether their specimen should be used in research, and the ability to use that specimen in the broadest and most beneficial way for society at large. Participants would be informed about potential risks for research that is most likely to yield identifiable results, therefore more appropriately tailoring regulation to risk and respect for persons. In this case, inclusion in the general healthcare consent of the broad research consent language which the agency plans to develop should be sufficient for future research use. Institutions should have the ability to modify broad consent language as necessary to address a range of future uses and populations.

⁷ Retrieved from: http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf

5. Public comment is sought regarding any concerns that you have about each of the three proposals, including concerns about implementation or burden to investigators and institutions.

Response: As stated above, biospecimens should not be included in the definition of human subject under the rule. Any special considerations for biospecimens should be covered under separate guidance.

Alternative A is the most acceptable and a justification for consent can be made for this Alternative. However, the requirements for consent (and data security) under Alternative A should be based on the intent to create a whole genome data set and the maintenance of that set rather than on use of the biospecimen itself. Furthermore, sharing a subset of that genome data without individual subject identifiers should be considered non-identifiable (and, hence, not meeting the definition of “human subject”) and not be subject to any further consideration under the rule.

Alternative Proposal B is not appropriate, as it proposes to define a human subject based on analytical technologies rather than on individuals. Given that the use of a technology, in and of itself, does not render materials identifiable, this is not an appropriate standard. While a technology may have the capability of generating information unique to an individual, the rule should not apply unless generating that information is a specified purpose of the research as in the case of whole genome sequencing. The modifier “may be readily ascertained” in the definition of private identifiable information within the definition of human subject is useful, as it allows for changes in scientific technology and data sharing over time and for assessments to be made in real time.

Alternative C, which is the treatment of biospecimens as currently written in the NPRM, is wholly inappropriate. The summary at the beginning states that, “the NPRM seeks to avoid requirements that do not enhance protection and impose burden, which can decrease efficiency, waste resources, erode trust, and obscure the true ethical challenges that require careful deliberation and stakeholder input. Cumbersome and outdated regulatory standards overwhelm and distract institutions, IRBs, and investigators in ways that stymie efforts to appropriately address the real risks and benefits of research.” This proposed treatment of biospecimens embodies burden, a decrease in efficiency, wastes significant resources, and will overwhelm institutions, IRBs, and investigators. This alternative comes at a significant cost to research, our understanding of disease, and the development of new therapeutics without improving protections. By requiring consent for all specimens, irrespective of the original purpose of the specimen collection, (and by caveat, removing specimens from biorepositories if an individual wished to later revoke consent for use), it establishes a requirement to maintain linkages to identifiers for all biospecimens even if there is no reason to do so other than to document informed consent. This, in and of itself, creates greater vulnerability for identification than the genetic materials contained within samples. Further, it requires the development of costly and extensive data security systems when they would otherwise be unnecessary.

6. Public comment is sought for whether this excluded activity should simply be discussed in the text of the final rule’s preamble, and guidance produced to assist investigators in making such a determination, or whether any other similar exclusions should be addressed.

Response: Yes, these excluded activities could simply be discussed in the text of the final rule’s preamble and guidance produced to assist investigators in making a determination. If, as proposed, investigators are going to make the exclusion determination without input from the IRB, clear and

concise guidance as well as educational materials will be essential. OHRP could consider developing a tool for investigators to determine what “excluded research” is. As currently written, some of the exclusions are sufficiently nuanced that many investigators might be confused about the meaning and lost in the nomenclature and Code of Federal Regulations (CFR) references. One approach would be to provide investigators with a robust decision tree in order to facilitate compliance with this element. In fact, one decision tree resulting in either an exclusion or exempt determination (or indicating that some form of review is needed) would help investigators to determine the correct category of research. If a decision tool is to be developed, however, one tool should be agreed upon by all of the sponsoring agencies. In addition, the agencies must involve research administration professionals in developing such a tool so that it has field-friendly workability and it should be validated by stakeholders (the FDP would be a valuable resource for testing its usefulness). Finally, investigator responsibility needs to be stressed. Any human subjects protection plan must rely on the ethical conduct of the investigators involved.

The decisions produced by the tool will only be as good as the tool and the materials and guidance that accompany it. To the extent institutions are not engaged in the process, institutions should not be held accountable for any unintended outcomes. It is unlikely, however, that the use of a federal decision tool would shield the institution or investigator from liability in third party actions

7. Public comment is sought for whether biospecimens should not be included in any of these exclusion categories, and if so, which ones.

Response: We see no reason not to include biospecimens in any exclusion category. We strongly support the position put forth by the National Academy of Science’s 2015 report, “Optimizing the Nation’s Investment in Academic Research: A New Regulatory Framework for the 21st Century: Part 1” which endorses the current standard that non-identifiable biospecimens collected for purposes other than research should continue to be excluded from coverage under the Common Rule. We agree with the Committee’s findings that “requiring consent for all research involving biospecimens would substantially increase administrative burdens on investigators, research staff and institutions” and “markedly hinder the conduct of critical science” and assert that it would not increase human subjects protections. Secondary research use of non-identified biospecimens and of biospecimens collected for non-research purposes should continue to be excluded from the Common Rule.

8. Public comment is requested on whether the parameters of the exclusions are sufficiently clear to provide the necessary operational guidance, or whether any additional criteria or parameters should be applied to clarify or narrow any of these exclusions.

Response: Since the intent is for investigators to make exclusion determinations without input from IRBs or other institutional resources, the exclusions are, as currently written not sufficiently clear. Any sections of the Common Rule which are to be interpreted and applied by individual investigators, who are generally not attorneys or regulatory experts, without IRB review (e.g., Excluded and Exempt) should be written to the same standard which the Rule requires for Informed Consent, *“The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. ...”* For example, the following sentence comes from the Excluded Research section of the NPRM: *“All of the following exclusion categories apply to research subject to this policy and to research subject to the additional requirements of 45 CFR part 46, subparts B, C, and D, however, the exclusion at paragraph (b)(2)(i) of this section applies only to research subject to subpart D for research involving educational tests, or observations of public behavior when the*

investigator does not participate in the activities being observed.” Or “Research as defined by this policy that involves only data collection and analysis involving the recipient’s use of identifiable health information when such use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of ‘health care operations’ or ‘research’ as those terms are defined at 45 CFR 164.501 or for the purpose of “public health activities” as described under 45 CFR 164.512(b).” These sentences, in addition to several other sections, do not meet the standard which the agency requires investigators and IRBs to meet regarding the Informed Consent. If the language in the Common Rule (or more specifically, the decision tool) does not adhere to this standard of being understandable by someone not specifically trained in legal or regulatory matters, it is not reasonable to expect that it will be properly applied by independent investigators.

9. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects.

Response: No, covering these activities under the Common Rule would not substantially add to the protections provided to human research subjects. We agree that these activities should be excluded from the regulations. They should be stated as examples, however, as the definition of those activities that do not constitute human subjects research are likely to be more numerous than those listed. We also note the following:

- We continue to maintain that non-identified biospecimens should be retained in the exclusion category.
- The exclusion of Quality Assurance or Improvement activities should not be limited to those where the purpose is to alter the utilization of an accepted practice. Comparative assessment of alternative practices to determine relative effectiveness should continue to be excluded from the regulations. Quality improvement goals in healthcare facilities would otherwise be impeded and burden and cost greatly increased without a resultant increase in the protections afforded patients. These activities are primarily based on the principles of epidemiology and surveillance and are outside the scope of the Common Rule.
- Regarding “activities that are excluded because they are considered to be low risk,” we believe that the exclusion of research involving the collection or study of information which is either publically available or non-identifiable, will be helpful in eliminating a set of studies from IRB consideration. The fourth such exclusion, however, requires that an investigator receiving public health information (PHI) from a covered entity needs to be from a covered entity as well. This is an unnecessary stipulation as the HIPAA Privacy Rule already requires the IRB to determine that the recipient will protect the identifiers from improper use and disclosure, has an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, and has given adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, unless required by law or by oversight of the research by a regulatory agency.

10. Public comment is sought on whether this exclusion should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, please comment on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, ability to opt-out, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: There is no mechanism for requiring notice to prospective subjects. If these studies are excluded from the regulation, then institutions will not have knowledge of their existence, and will have no means of assuring that such procedures are in place. If notice is a condition of conducting “excluded” research, then it is not, in fact, excluded. By its very definition, “excluded” research is not subject to requirements of the Rule. And, therefore, institutions should not be held accountable for whether an investigator gave any kind of notice. We would suggest that notice isn’t necessary and if OHRP deems it necessary the activity should not be excluded but rather added to the Secretary’s list of minimal risk research that qualifies for expedited review.

11. Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

Response: As stated in answers above, if research is “excluded,” then it should not be subject to the regulation. If there is a determination that record retention requirements must be in place, then the regulation should be changed to state that the categories for which records must be kept are not “excluded” but fall into some other category. Also as stated above, it is not reasonable to rely on investigators to make self-determinations with the complex language currently found in the proposed rule. The rule must be written in a way which is much clearer to individuals not accustomed to working with the law and regulations if it is expected that investigators can reliably apply the standards incorporated herein. A tool, as is proposed for exempt research, could assist investigators in making these decisions independently. And, finally, investigator responsibility should be stressed. Institutions cannot be responsible for exclusion determinations made solely by investigators. If a decision tool incorporated exclusions as well as exempt determinations, then retention of the exclusion determination by the investigator should serve as a sufficient record.

12. Public comment is sought regarding whether some or all of these activities should be exemptions rather than exclusions.

Response: In order to achieve the stated goal of regulatory burden reduction, it is important that these categories be exclusions.

13. Public comment is sought regarding whether these exclusions should be narrowed such that studies with the potential for psychological risk are not included. Are there certain topic areas of sensitive information that should not be covered by this exclusion? If so, please provide exemplary language to characterize such topic areas in a manner that would provide clarity for implementing the Rule.

Response: We believe that the exclusions should not be narrowed.

14. For activities captured under the third element of this exclusion, do the statutory, regulatory, and other policy requirements cited provide enough oversight and protection that being subject to expedited review under the Common Rule would produce minimal additional subject protections? If so, should the exclusion be broadened to also cover secondary analysis of information collected pursuant to such activities?

Response: Yes, the other, existing statutory, regulatory, and other policy requirements provide adequate oversight and protection. Therefore, these activities should continue in the excluded category. Because of the very significant protections that these regulations provide (e.g., HIPAA), the exclusion should be broadened to cover secondary analysis. We object, however, to the exclusion requiring that an

investigator receiving PHI needs also to be from a covered entity. This is an unnecessary stipulation because the receiving investigator would be required by the donor institution to apply HIPAA safeguards to protect the confidentiality of the PHI.

15. Public comment is requested on the extent to which excluding any of these research activities from the Common Rule could result in an actual or perceived reduction or alteration of existing rights or protections provided to human research subjects. Are there any risks to scientific integrity or public trust that may result from excluding these research activities from the Common Rule?

Response: We believe that excluding these research activities from the Common Rule is both reasonable and advisable. It will not reduce the rights and protections provided to human research subjects nor do we believe it will present risks to scientific integrity or public trust.

16. Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

Response: Guidance and educational materials for all excluded categories will be needed if investigators, not IRBs, are making these determinations. We do not see a need to set-apart this exclusion category from others. A decision tool may also assist investigators in making the correct decision about whether research is excluded, exempt, or requires some form of review. Since this category is excluded from the regulation, we do not believe it is appropriate to impose regulatory requirements regarding documentation or record retention for this or other excluded categories. To do so would be contrary to the concept of “excluded” and would bind the institutions to verify such records are kept increasing cost and burden.

17. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects. Is there a way in which this exclusion should be narrowed? Public comment is also sought regarding whether activities described here should appear as an exclusion or as an exemption.

Response: Regarding research involving the collection or study of information that has been or will be collected, the nature of the research as well as the data captured/omitted in this research make it, and other items proposed for exemption, appropriate for inclusion as excluded research and it should not be narrowed. Information that is already publicly available or has been rendered non-identifiable should not be subject to additional protections.

18. Public comment is sought on whether this or a separate exclusion should also include research involving information collected for non-research purposes by non-federal entities where there are comparable privacy safeguards established by state laws and regulations, or whether such non-federally conducted research would be covered by the proposed exemption at § 11.104(e)(2).

Response: The exclusion and exemption categories as written in the NPRM are adequate with the exception that we continue to maintain that non-identified biospecimens should be retained in the exclusion category as is the case in the current regulation.

19. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects.

Response: Coverage under the Common Rule is not needed.

20. Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

Response: Additional clarity is needed for investigators to make these determinations. For example, clarity is needed as to whether or not data collected under this excluded category for research by federal departments or agencies can then be excluded if used for secondary research purposes by non-federal employees. It is not reasonable to require documentation for something that is not subject to regulation.

21. Public comment is sought regarding whether some or all of these activities should be exemptions rather than exclusions.

Response: They should remain exclusions.

22. Public comment is requested on whether the protections provided by the HIPAA Rules for identifiable health information used for health care operations, public health activities, and research activities are sufficient to protect human subjects involved in such activities, and whether the current process of seeking IRB approval meaningfully adds to the protection of human subjects involved in such research studies.

Response: HIPAA protections are sufficient. In situations where research disclosures or waivers under HIPAA require institutional review, it is commonly assigned by the institution to IRBs. Therefore in these cases, the IRB will review for compliance with HIPAA and additional protections are not necessary. The current IRB practices provide this protection and no additional requirements are necessary.

23. Public comment is sought regarding to what extent the HIPAA Rules and HITECH adequately address the beneficence, autonomy, and justice aspects for the collection of new information (versus information collected or generated in the course of clinical practice, e.g., examination, treatment, and prevention). Should this exclusion be limited to data collected or generated in the course of clinical practice? If additional data collection is allowable, should it be limited to what is on the proposed Secretary's list of minimal risk activities (discussed in more detail below in II.F.2 of this preamble)?

Response: HIPAA Rules and HITECH adequately address the Belmont Principles with respect to this section of the Common Rule exclusions. No further restrictions or limitations should be added.

24. Public comment is requested on whether additional or fewer activities regulated under the HIPAA Privacy Rule should be included in this exclusion.

No Response.

25. Should research involving prisoners be allowed to use any or all of the exclusions found at § ll.101(b)(2) and (3), as currently proposed?

Yes.

26. Are there certain provisions within the broader categories proposed at § ll.101(b)(2) and (3) to which the subparts should or should not apply?

No.

27. Public comment is sought regarding how likely it would be that institutions would allow an investigator to independently make an exempt determination for his or her own research without

additional review by an individual who is not involved in the research and immersed in human research protection e.g., a member of the IRB Staff.

Response: This question illustrates one key way in which this NPRM is not adequately developed at this time. It is impossible to comment on whether or not institutions will allow an investigator to independently make exempt determinations using a tool developed by the agency(ies) when such a tool does not yet exist. The answer depends on the tool, its validation, the nature and scope of training required for the tool to be used properly, and the liability of the institution if/when the tool is not used properly. The “safe harbor” comes with a key stipulation that the tool must be completed accurately. This relies on criteria outlined above: a) the regulation being clear to individuals not trained in the law or regulatory compliance, b) the existence of a validated decision tool, and c) the nature and extent of training.

The Exempt Wizard, a tool for researchers to self-determine exempt status, was developed by faculty at a COGR institution in consultation with OHRP as a Federal Demonstration Partnership (FDP) project. Although we believe it has promise, the Wizard was not widely used and not extensively tested. It was also developed under the existing Common Rule, so any pilot data do not apply to its utility with the proposed, more complex and nuanced Rule. It is impossible for us to evaluate any proposed decision tool which has yet to be developed or validated. As noted in our introduction, we recommend that language and questions pertaining to the proposed tool be removed from the NPRM, that a tool be developed and tested in cooperation with the research community, and that a notice be republished separately once such a tool is developed.

In theory, we support the concept of a tool developed by the federal government which would serve the same purpose as the Wizard. Our qualified approval comes with several important provisos:

- 1) For simplicity and consistency, one tool should be agreed upon by all of the sponsoring agencies.
- 2) The agencies must involve research administration professionals in developing such a tool so that it has field-friendly workability.
- 3) The tool should be validated by institutions and investigators (the FDP would be a valuable partner in this undertaking).
- 4) The decisions produced by the tool will only be as good as the tool and the materials and guidance that accompany it. To the extent institutions are not engaged in the process, institutions should not be held accountable for any unintended outcomes. It is unlikely, however, that the use of a federal decision tool would shield the institution or investigator from liability in third party actions.
- 5) Clear indication that the tool determines exemption from federal regulations and state restrictions still apply.

28. Public comment is sought regarding whether an investigator would be able to contrive his or her responses to the automated exemption decision tool in order to receive a desired result i.e., an exempt determination, even if it does not accurately reflect the research activities.

Response: This is impossible to answer until the tool is available to review. All of the policies involving ethical considerations in research depend upon the truthfulness and benevolent intentions of investigators. Deliberately answering questions incorrectly, whether in a full IRB review or in an exempt or exclusion tool will always result in a false outcome.

29. Public comment is sought on whether it would be more appropriate for some of the exempt

categories than others to rely on the exemption determination produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances.

Response: Again, without the tool this is impossible to answer. The key is in the way the tool is designed. If it simply lists the exempt categories, if the Rule remains as currently proposed, it will not easily be understood. If, on the other hand, it asks a series of appropriate questions about the nature of the project, the data to be collected, and the methods of collection and storage, it might be appropriate. Developing an adequate tool is a major undertaking which apparently has not been possible to accomplish in the four years since the issuance of the ANPRM.

30. Public comment is sought regarding whether relying on the exemption determination produced by the decision tool where investigators themselves input the data into the tool as proposed would reduce public trust in research.

Response: The entire system of human subject research is based on trust in investigators along multiple dimensions. A well designed, tested and validated tool could actually enhance the public trust.

31. Public comment is sought regarding how likely it would be that institutions would rely on such a decision tool to provide a safe harbor for an investigator making a determination that the proposed research qualifies for an exemption, or whether developing such a tool would not be worthwhile, and whether institutions would be able to adequately manage exemption determinations without the use of the decision tool.

Response: A good tool would be useful, irrespective of whether the investigator or the institution made exempt determinations. As stated above, the safe harbor for investigators does not address the key issue that agencies currently hold institutions responsible for activities such as this. We believe, instead, that investigator responsibility in this area should be stressed. Institutions would be able to adequately manage exemption determinations without the use of the decision tool as they currently do, although it would not reduce current administrative burden to do so.

32. Public comment is sought regarding what additional information should be required to be kept as a record other than the information submitted into the decision tool, for example, a study abstract, the privacy safeguards to be employed, or any notice or consent document that will be provided.

Response: The tool should be designed in a way that elicits all of the information required in order to make the exempt determination and which identifies the researcher and title of the project. No other information should be required. Exempt research means that it is not subject to the requirements of the policy. If you are going to require privacy safeguards or notice or consent, then the research is not exempt and should not be included in that category.

33. Public comment is sought regarding the value of adding an auditing requirement.

Response: Auditing should be restricted to higher risk research. By the very nature of the low risk associated with exempt research, assigning resources to audit these studies will reduce resources which should be focused on higher risk studies. This is a task that should be left to the discretion of the institution to weigh burden and risk.

34. Public comment is sought on whether this exemption category should only apply to research activities in which notice that the information collected will be used for research purposes is given to prospective subjects or their legally authorized representatives as a regulatory requirement, when not

already required under the Privacy Act of 1974. If so, comment is sought on what kind of information should be included in the notice, such as the research purpose, privacy safeguards, contact information, etc. Comment is also sought on how such a notice should be delivered, e.g., publication in a newspaper or posting in a public place such as the school where the research is taking place, or by individual email or postal delivery. Note that other requirements, such as those of the Family Educational Rights and Privacy Act (FERPA) or the Protection of Pupil Rights Amendment, may also apply. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: As a basic principle, exempt research should mean that the category of activity is exempt from the regulation. If the agency determines that a category of research requires notice with stipulated elements, then this is no longer an “exempt” category of research. It is essential for clarity to the research community that any requirements or obligations be consistent within categories of research. This is particularly true in categories (excluded and exempt) where the agency is proposing independent decisions by investigators.

35. Public comment is sought on whether the privacy safeguards of § 11.105 should apply to the research included in § 1.104(d)(1), given that such research may involve risk of disclosure of identifiable private information.

Response: As stated above, if a category of research is exempt, then it should be exempt from all sections of the rule.

36. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice, e.g., the research purpose, privacy safeguards, or contact information. Also comment on how such a notice should be delivered; e.g., publication in a newspaper or posting in a public place, or by individual email or postal delivery. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence? In many cases, it may be that individual notice or consent to all potentially affected persons before the research or demonstration commences is ordinarily impossible in the conduct of such studies. For example, if a research or demonstration project will affect all inhabitants of a large geographic area (e.g., a housing, a police patrol, a traffic control, or emergency response experiment), or all clients or employees of a particular program or organization or setting will be subject to a new procedure being tested (e.g. a new approach to improving student performance, a new anti- smoking or anti-obesity program, a new method for evaluating employee performance), would it be possible to make participation voluntary for all affected individuals, or even to identify and inform all affected individuals in advance?

Response: As stated above, if a category of research is exempt, then it should be exempt from all sections of the rule.

37. Public comment is sought on whether this exemption category is appropriate based on the recognition that alternative processes are in place in which ethical issues raised by research in public benefit or service programs would be addressed by the officials who are familiar with the programs and responsible for their successful operation under state and federal laws, rather than meeting specific risk-based criteria, or whether risk limitations should be included, and if so, what those limitations should be. Though long-standing, this exemption has never identified specific risk-based criteria, or

risk limitations to bound the type of projects that may be covered. When originally promulgated, the exemption did stipulate that following the review of such projects, if the Secretary determines that the research or demonstration project presents a danger to the physical, mental, or emotional well-being of a participant or subject, then written informed consent would be required. Public comment is sought on whether to limit the risk that can be imposed on subjects while using this exemption, and if so, how to characterize those limits in a clear fashion. If more than minimal risk interventions are included, public comment is sought on whether, for transparency, this should be made clear in the regulatory text.

With regard to the issue of risks encountered by participants in such research or demonstration projects, comments are also sought regarding the argument that any and every demonstration project involving changes in public benefit or service programs (e.g., water or sewage treatment programs or pollution control programs, programs involving educational procedures, or programs involving emergency procedures related to extreme weather events, etc.) exposes those affected to possible risks of some kind. In this regard, those risks are ordinarily and perhaps always no different in kind or magnitude than those involved in simply making the change in procedures without using research tools to evaluate them. For example, health care providers could be required to perform certain sanitation reforms to prevent patient infections whether or not such reforms were first tested in practice through a research or demonstration project. It is common for all Federal departments and agencies that regulate private or public organizations to impose conditions of participation in public programs providing for safety, program integrity, financial reporting, etc. Public comment is sought regarding whether there should be conditions (e.g., an individual notice or consent requirement) imposed on such research or demonstration projects involving public benefit or service programs which might lead to significant impediments or limitations on testing and evaluation before or after being imposed program-wide. Would the effect of imposing expensive or impracticable conditions on public benefits or services evaluations be to reduce the number of such evaluations and consequently to expose program participants to increased risk through exposure to untested reforms?

Response: Additional requirements should not be imposed on this exempt research.

38. Public comment is sought on whether the existing privacy safeguards for such activities, including the Privacy Act, HIPAA rules, and other federal or state privacy safeguards provide sufficient independent controls, or whether other safeguards such as the privacy safeguards of § 11.105 should be applied.

Response: Existing safeguards are sufficient.

39. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice, such as the research purpose (if authorized deception is not utilized), privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: Additional requirements should not be imposed on this exempt research. Since the concept of exempt research is that it will not be reviewed by an IRB, if a notice were required, it must be a standard notice developed by agencies and available for use by investigators. Such a notice would need to carry the agency's "safe harbor" standard as being acceptable without modification if the rule is going to require its use.

40. Public comment is sought regarding what improvements could be made to the language describing the type of interventions in this exemption category so as to make clear what interventions would or would not satisfy this exemption category.

Response: This question demonstrates, again, that this regulation is not in a form that is ready for implementation. A NPRM should be in a format upon which the public can comment rather than being a document needing further development to the extent that public input is sought to design the regulation. The key to this and other exempt questions is that the decision tool provided by the agency will need to distinguish the nature of the research rather than simply providing a listing of interventions which can never be complete.

The new exemption involving what is now called “benign interventions” should be renamed to better reflect its nature. The meaning of these two words commonly connote medical procedures, but are being used here to describe social and behavioral sciences studies. They are not benign in the sense that they are beneficial to the subject, but are rather, neutral in that they will not convey harm. They are also not “interventions” in the conventional sense, but rather, interactions with the investigator or computer to perform certain tasks. Similar to the privacy safeguards, above, this exemption adds another burden to the IRB review in that it requires the subject’s prospective agreement to the intervention and data collection. We also believe it would be helpful to include marketing studies in this category and that the list be framed as examples rather than being prescriptive.

41. Public comment is sought on whether it is reasonable, for purposes of this exemption, to rely on the exemption determination produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances.

Response: Again, without seeing and evaluating the tool it is impossible to answer this question. We recommend that language and questions pertaining to the proposed tool be removed from the NPRM, developed and tested in cooperation with the research community and republished separately once developed.

42. Public comment is sought on whether this exemption category should be narrowed to apply only to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: The nature of this research is such that a notice containing specified elements should not be required.

Should prospective subjects be given the explicit opportunity to opt out of such research?

Response: Subjects should always be provided the opportunity to opt out if there is a notice. This is inherent in human subject research ethics. If a notice is not required, then there is no formalized way to opt-in or opt-out.

43. Public comment is sought on the concept of requiring such minimum safeguards and limitations on disclosure, as well as whether the requirements of the proposed § 11.105 would constitute a broadening of IRB responsibilities rather than a streamlining of the implementation of responsibilities that many IRBs already adopted. If an institution does view this as an inordinate broadening of responsibilities,

does the institution currently have in place alternative mechanisms for ensuring data security and participant privacy in a research context? Suggestions for alternative approaches to meeting public expectation that federally sponsored research safeguard their data and protect privacy are sought during this public comment period.

Response: We note that in a summary of ANPRM comments presented to SACHRP in February 2012, a “strong majority” opposed the use of data security and information protection standards modeled on the HIPAA rules and to additional data security standards (for exempt research). IRBs currently evaluate data security in the context of the nature of the research and information collected and stored. Therefore, a wide range of options are available which are scaled appropriately under the approval of the IRB and security standards continue to be enhanced to effectively protect research information.

It is not possible to evaluate proposed safeguards because the agency security standards are not provided. We strongly recommend that the data security requirements for all data except those currently covered by HIPAA be removed from the NPRM until such time as the agency provides a complete proposal for alternative standards which can be appropriately reviewed by both the research and information technology (IT) communities and applied only when the data being secured warrants such protection.

The NPRM suggests that, once the safeguards list is developed and issued, it will be open to public comment, and that there will be flexibility regarding the application and implementation of the data security safeguards. We suggest that safeguards should be manifested as tiered levels of data security protection corresponding to the level of risk. In drafting the data security safeguards, the Secretary should consider the robust data security policies and procedures developed at institutions and allow for adherence to such policies. Defaulting to the decidedly less flexible HIPAA standards would be inappropriate for the wide range of research activities subject to the Common Rule. The HIPAA regulations do not cover de-identified specimens and conflict with the NPRM’s proposed limits on the use and disclosure of identifiable data and biospecimens. The HIPAA standard should only be employed when protected health information is involved in the research. OHRP should clarify that HIPAA covered entities are not required to expand HIPAA to meet the .105 standard.

44. Public comment is sought regarding whether the proposed Rule’s information security requirements for biological specimens and identifiable private information are highly technical and require a level of expertise not currently available to most IRBs. Do these security requirements unrealistically expand IRB responsibilities beyond current competencies?

Response: Although it is difficult to comment on security standards the agency has not provided, we believe any proposed security requirements would not unrealistically expand IRB responsibilities beyond current competencies. IRBs currently work in partnership with the institution’s IT specialists and this relationship works well. IRBs determine the sensitivity and necessary level of protection and IT assesses the technical requirements of the proposed safeguards. IRBs do not have to know or understand the technical requirements of IT systems for HIPAA and other compliance. This is managed for the covered entity’s records by IT security professionals.

45. Public comment is sought on whether the proposed exemption regarding the use of educational tests, survey procedures, interview procedures, or observation of public behavior (§ 11.104(e)(1)) should be applied to research involving the use of educational tests with children and whether it should also be applied to research involving the use of survey or interview procedures with children. If so, for research

involving children, should the permissible survey or interview topics be limited in some way?

Response: Educational testing with children is appropriate under this exemption. However, survey or interview procedures involving sensitive information should not include children under this exemption.

46. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

Response: Notice is not necessary. Since the concept of exempt research is that it will not be reviewed by an IRB, if a notice were required, it must be a standard notice developed by agencies and available for use by investigators. Such a notice would need to carry the agency's "safe harbor" standard as being acceptable without modification if the rule is going to require its use.

Should prospective subjects be given the explicit opportunity to opt out of such research?

Response: If you require that notice be given, subjects should always be provided the opportunity to opt out. This is inherent in human subject research ethics.

47. Public comment is sought on whether it is reasonable, for purposes of this exemption, to rely on the exemption determinations produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances?

Response: It is not possible to answer this question without the ability to evaluate the tool. Parts of the NPRM specific to the decision tool should be removed. HHS should solicit public comment on the tool and its use in assisting with exclusion determinations once it has been developed.

48. Public comment is sought on whether this exemption category should be narrowed such that studies with the potential for psychological risk are not included. Are there certain topic areas of sensitive information that should not be covered by this exemption? If so, please provide exemplary language to characterize such topic areas in a manner that would provide clarity for implementing the Rule.

Response: It is not possible to delineate a definitive list of sensitive information which would trigger negative psychological reactions. Under the rule as written, this would have to be left to the professional discretion of the investigator. If the agency believes that this category of research cannot be properly evaluated by the investigator independently or incorporated into the decision tool, it should not be included in the exempt listing.

49. Public comment is sought on the types of research that should fall under the proposed exemption. Should the proposed exemption be available to all types of research using identifiable data collected for non-research purposes or should the exemption be available only to a more limited subset of research? For example, should the proposed exemption apply only for research using records and information already subject to comprehensive privacy and other protections in other Federal laws (e.g., records held by the Federal Government subject to the Federal Privacy Act, or records governed by HIPAA or FERPA)? Depending upon the scope of the exemption, the relationship between this exemption and the exemption proposed at § ll.104(f)(2) would need to be clarified. Since a major justification for including this exemption is to reduce burden on IRBs, should the proposed exemption apply only to research for which IRBs typically waive informed consent, that is, where the research could not

practicably be carried out without a waiver of informed consent, and the rights and welfare of subjects will not be adversely affected by the waiver? Finally, is there a sufficient need for this exemption at all given the other proposed exclusions and exemptions?

Response: As you state in your question, IRB waiver of informed consent is frequently sought for this category of research. 104(e)(2), as written, will not reduce IRB burden because the exemption requires prior notice of the specific research. This is a much higher standard than under the current rule, and will make this exemption difficult to use.

50. Public comment is sought regarding whether the proposed exemption should be limited to research in which individuals had been informed of the potential future research use of their information, and given the opportunity to opt out of having their identifiable private information used for research. If the proposed exemption should be limited in this way, what information should be included in the opportunity to opt out? If the opportunity to opt out is made a condition of the exemption category how should it be structured (e.g., how long and under what circumstances should it remain in effect) and what, if any, impact should the opt out have on other provisions of the rule, such as the ability of an IRB to waive informed consent for a subsequent research study using the individual's information? Are there other or alternative mechanisms that should be required to respect individuals' autonomy and other interests?

Response: The concept of requiring an opt-out option is a simple concept to articulate and an extremely complex and costly concept to implement. Given that much of the information sought under such an exempt category is already subject to regulations such as HIPAA and FERPA, this requirement is not necessary, as those regulations already have mechanisms to protect the interests of individuals. Consideration of a time limit for opt-out consent to remain in effect adds even greater data management complexities. We believe that few institutions will incur the costs of implementing such complex and costly changes in their data systems, and this exemption, therefore, would be rendered useless.

51. Public comment is sought regarding what should constitute notice for purposes of this exemption category. Given the many different types of data that would be covered by this provision (e.g., data from private entities used for social or behavioral science research, government records for which laws already establish standards for notice, and data publicly available for harvesting from the internet), would it be possible to develop a uniform "notice" requirement? What type of notice, in terms of its dissemination and scope, should be considered to meet this requirement of the proposed exemption? With regard to the dissemination of the notice, should the notice requirement be permitted to be fulfilled through a general public notice, not specifically directed to individuals who are potential research subjects, such as the notice allowable under the Privacy Act? Would a prominent notice posted in all clinics or other relevant public places where information will be collected be acceptable? Should each individual whose data could be used receive their own notice, such as is required of direct treatment providers covered by the HIPAA Privacy Rule? With regard to the content of the notice required by this proposed exemption, what kind of information should be included in the notice, such as the types of research that might be conducted, privacy safeguards, contact information, etc.?

Response: Notice should not be required. This series of questions demonstrates the many difficulties in responding to this NPRM. First, "data publicly available for harvesting from the internet" is listed above as an example but is also listed as a criterion for excluding research from the Common Rule. Which is the intention of the agency? Furthermore, this question does not ask for comment but actually asks the

community to construct the tools and requirements to embody within the rule. The fact that these questions are now being asked speaks to the unresolved complexities embodied within the NPRM.

52. Public comment is sought on whether, on the other hand, prior notice is necessary. Is the notice requirement proposed for this exemption a meaningful and important measure to respect individual autonomy, particularly if the notice requirement could be fulfilled through a general public posting? Current practices suggest that IRBs will frequently waive informed consent for studies involving the secondary use of identifiable private information collected for non-research purposes. If the exemption were to exclude the notice requirement, but continue to require application of the data security and privacy safeguards of § 11.105 and restrict the use of identifiable private information to only purposes of the specific research for which the investigator obtained the information, would the exemption better strike a reasonable balance between respect for persons and beneficence, while eliminating the current requirement for IRB review?

Response: Given that IRBs frequently currently waive consent, there is no justifiable reason to add the notice requirement. However, keep in mind that IRBs commonly function as the Research Privacy Board under HIPAA, so this may not eliminate the requirement for Board review. The data security and privacy rules should not apply to this, as data which require specific treatment, such as patient records, are already covered under appropriate regulations. If the investigator wishes to use the information for secondary research, such activities would presumably require re-evaluation for use as excluded, exempt or covered under the Common Rule and would have to follow the appropriate rules as apply.

53. Public comment is sought as to whether this exemption would provide appropriate protections for research conducted by clinical data registries, while enabling these research activities to proceed without delay, and what should be included in guidance regarding such activities. Public comment is sought regarding the extent to which other exclusions or exemption categories would apply to research conducted by clinical data registries, such that the conditions of this exemption category would not apply.

Response: Submission of information to clinical data registries will be evaluated under HIPAA regulations, so there is no reason to apply additional requirements.

54. Public comment is sought on whether the NPRM's proposal of exemption § 11.104(f)(2) is the best option, or whether there is a better way to balance respect for persons with facilitating research.

Response: Research involving the use of biospecimens that have been stored or maintained for secondary research use should continue to be exempt without consent. Legislation that addresses unauthorized re-identification, institutions' security safeguards, and greater effort to educate the public about the risks and scientific value of genetic studies involving secondary use of biospecimens (e.g., development of innovative diagnostics, treatments, cures or preventative interventions) would more effectively balance privacy and autonomy concerns with facilitating research.

55. Public comment is sought on whether and how the provision regarding the return of research results in the proposed exemption § 11.104(f)(2) should be revised.

Response: The federal government should not establish a panel of experts to make determinations about returning unexpected findings to subjects. Such a bureaucratic apparatus would immediately become bogged down in not only volume but many unnecessary aspects of research. It would do

nothing to reduce overall regulatory burden and will delay research progress with questionable added value to protection of subjects.

The NPRM does not make clear why the research cannot remain exempt if results are returned to the subject. This is in particular the case, if the results are provided by a licensed healthcare provider. As the NPRM points out, “IRBs do not have any particular unique expertise in making these determinations.” However, licensed healthcare providers do. Just as these individuals make decisions about returning specific results from a number of general laboratory tests in the patient care setting, they are qualified to do the same with clinically important research findings. We see no reason why the research cannot remain exempt if results are returned to the subject.

56. Public comment is sought on whether there should be an additional exemption that would permit the collection of biospecimens through minimally invasive procedures (e.g., cheek swab, saliva).

Response: Yes. Such minimally invasive procedures should be treated in the same regard as collecting general information. The fact that they are biospecimens should not set them apart.

57. Public comment is sought on whether research involving prisoners should be permitted to apply any or all of the exemption categories found at proposed § ll.104, either if the research consists mostly of non-prisoners and only incidentally includes some number of prisoners, as proposed in the NPRM, or if the research intends to involve prisoners as research subjects.

Response: The exempt categories should stand and the inclusion of prisoners be allowed in cases where the research consists mostly of non-prisoners and only incidentally includes some prisoners. If the research intends to involve prisoners as research subjects then the exemption categories in 104 should stand except in the following situations: a) Studies covered under 104(e) which involve the collection of sensitive information when subjects can be identified directly or through identifiers linked to the subjects, and b) Any collection, use and storage of biospecimens if the final Common Rule requires an identifiable linkage between biospecimens and individuals to allow investigators the ability to document consent for all biospecimens.

58. Would it be preferable for language at § ll.104(b)(2) to resemble the 2002 epidemiologic waiver criteria and state that the exemptions apply except for research where prisoners are a particular focus of the research?

Response: See the answer above in 57.

59. Is the proposed application of the exemptions to subparts B and D appropriate?

Yes.

60. What topics should be addressed in future guidance on improving the understandability of informed consent?

Response: The vast majority of consent information is required by regulatory agencies. In fact, one of the most common reasons for the length of consent forms is the inclusion of standard-of-care information which regulatory agencies require be included as a component of foreseeable risks or discomforts. This information should be moved into an appendix and only the information regarding the truly experimental component (e.g., the IND under investigation) should be in the body of the consent. This change could occur immediately without a change in the regulation if OHRP and the FDA issued harmonized guidance to this effect. Common “non-essential” or “non-regulatory” elements

include information about investigators' outside financial interests and the inclusion of HIPAA disclosure information. The former is sound practice in keeping with OHRP recommendations, and the latter must appear somewhere in the process as required by law.

61. Public comment is sought on whether broad consent to secondary research use of information and biospecimens collected for non-research purposes should be permissible without a boundary, or whether there should be a time limitation or some other type of limitation on information and biospecimens collected in the future that could be included in the broad consent as proposed in the NPRM. If a time limit should be required, is the NPRM proposal of up to 10 years a reasonable limitation? Would a limitation related to an identified clinical encounter better inform individuals of the clinical information and biospecimens that would be covered by a broad consent document?

Response: Broad consent for secondary research use of information collected for non-research purposes should not be required for research which, otherwise, meets the criteria for exemption under 104. No additional limitation should be imposed for information collected in the future outside of limitations already imposed through other laws and regulations (e.g., HIPAA, FERPA). Biospecimens should be handled the same way as information, and broad consent should not be required for federally-funded research when the specimens were collected for other purposes.

There should be no time limits imposed as the NPRM proposes. The mobility of our society would make re-consent extremely costly and difficult to manage, thereby rendering large banks of information and specimens unusable after 10 years. This would dramatically impair long-term research.

62. Public comment is sought on whether all of the elements of consent proposed at § 11.116(c) should be required for the secondary use of biospecimens or identifiable private information originally collected as part of a research study that was conducted without consent because either the original research study met an exclusion or exempt category of research, or a waiver of consent was approved by an IRB.

Response: If the secondary research meets the criteria for exclusion or exemption, then consent should not be required. If it does not meet these criteria, then whether or not informed consent is required should be determined by the IRB. If the IRB determines that consent is required, then all elements of consent should be required.

63. Public comment is sought on whether oral consent should be permissible in limited circumstances as proposed under exemption

§ 11.104(f)(1).

Response: It is not clear whether or not the question is asking if oral consent may occur without IRB review and approval or if the IRB will need to make the determination as is described within 116. We believe that additional consent should not be required given the nature of the original research exempted under 104(f)(1). 104(f)(1) is extremely difficult to read and understand, and it is very unlikely that investigators will be able to consistently apply the requirements under this section properly.

64. Would research subjects continue to be appropriately protected if the definition of "legally authorized representative" were broadened to include individuals authorized by accepted common practice to consent on behalf of another individual to participation in clinical procedures? If the definition of "legally authorized representative" was broadened in this way, public comment is sought

on the interpretation of “accepted” and “common” as these terms would be used in the revised definition.

Response: Yes. The definition of “legally authorized representative” should be broadened to cover anyone accepted for providing such authorization for clinical procedures.

65. Public comment is sought on how the waiver criterion regarding “practicably” at § 11.116(d)(3) could be explicitly defined or otherwise clarified (e.g., what term should replace “practicably”?).

Response: The term “practicably” could be replaced with “reasonably feasible”; capable of being effective, done or put into practice so as to be feasible.

66. Public comment is sought on the proposed differences between the criteria for waiving informed consent for the research use of biospecimens versus identifiable information.

Response: We urge the agency to harmonize the criteria by applying the standard for identifiable information to biospecimens. There should not be a different standard and IRBs should have the ability to waive consent for research use of biospecimens as they do under the current rule.

We suggest that each research project should be viewed independently based on the merits of the scientific knowledge to be gained, weighed against respect for individuals’ rights to consent. IRBs have successfully managed this decision point for some time and have both the experience and ability to interpret the current waiver criteria within their ethical frameworks that allows important research to continue while protecting human subjects. No evidence is presented that this approach has compromised privacy for human subjects. If consent were sought in conjunction with a specific protocol, irrespective of how broad the consent might be, this should not trigger a prohibition on waiving consent for secondary research of biospecimens and identifiable information. This proposed change will reduce flexibility for the IRB and investigator and increase burden without increasing human subjects protections.

67. Public comment is sought on whether the proposal to permit an IRB to waive consent for research involving the use of biospecimens should be included in the regulations.

Response: Findings from an analysis of a random sample (300) of the 1100+ comments DHHS received in response to the ANPRM included in the article “Public Comments on Proposed Regulatory Reforms That Would Impact Biospecimen Research” published in the September/October 2015 issue of IRB Ethics and Human Research⁸ indicate that 70 supported waiver, 8 indicated qualified support, and 3 did not support the use of waivers. We also note that in the summary of ANPRM comments presented to SACHRP, a “very strong majority” favored allowing waiver of consent for the collection and study of existing data and biospecimens provided they are non-identified and met existing waiver criteria. Given the support for waiver of consent, we question why the NPRM proposes to make such waivers “rare.” We suggest that each research project should be viewed independently based on the merits of the scientific knowledge to be gained, weighed against respect for individuals’ rights to consent. IRBs have successfully managed this decision point for some time and have both the experience and ability to interpret the current waiver criteria within their ethical frameworks that allows important research to continue while protecting human subjects. No evidence is presented that this approach has compromised privacy for human subjects. If consent were sought in conjunction with a specific

⁸ Cadigan, RJ, Nelson, DK, Henderson, GE, et al. September-October 2015. Public Comments on Proposed Regulatory Reforms That Would Impact Biospecimen Research: The Good, the Bad, and the Puzzling. IRB Ethics and Human Research; 37(5). Retrieved from: <http://www.thehastingscenter.org/Publications/IRB/Detail.aspx?id=7554>

protocol, irrespective of how broad the consent might be, this should not trigger a prohibition on waiving consent for secondary research of biospecimens and identifiable information. This proposed change will reduce flexibility for the IRB and investigator and increase burden without increasing human subjects protections.

68. Public comment is sought on the proposal to permit an IRB to waive consent for the secondary use of biospecimens or information originally collected for research purposes, even if the original research study required subjects' informed consent.

Response: The IRB should be permitted to waive consent for secondary research under these conditions unless original research consent a) did not include the possibility of secondary research, b) informed the subject that secondary research would be limited in a way which does not include the newly proposed research, or c) contained an opt-out or opt-in section for subjects to indicate their willingness for the data or biospecimens to be used for future research.

69. Public comment is sought regarding how likely investigators are to seek broad consent for the use of identifiable private information (as contrasted with biospecimens), given that there are provisions within the NPRM that would make it easier to do such research without consent (such as the new exemption at § ll.104(e)(2)). In this regard, note that the NPRM proposal to prohibit waiver of consent by an IRB if a person has been asked for broad consent and refused to provide it might create a disincentive on the part of investigators from choosing to seek broad consent for research involving secondary use of identifiable private information. Given the costs and time and effort involved in implementing the system for obtaining broad consent for the use of identifiable private information and tracking when people provide consent or refuse to do so, are the benefits to the system likely to outweigh the costs, and if so, should the broad consent provisions be limited to obtaining broad consent for research use of biospecimens?

Response: The cost and complexities of maintaining broad consent records for both identifiable private information and biospecimens will be prohibitive to a wide range of research activities. Investigators will use the flexibility to avoid this process whenever the opportunity exists. We strongly encourage the elimination of the broad consent for both information and biospecimens.

70. Public comment is sought on the proposed prohibition on waiving consent when an individual has been asked to provide broad consent under § ll.116(c) and refused. In particular, how would this prohibition on waiving consent affect the secondary research use of identifiable private information?

Response: The series of questions posed under #70 demonstrate the extent of the difficulty involved in managing requirements for broad consent for both data and biospecimens. A key issue is whether or not a broad consent can be developed and administered which truly informs patients of the ramifications of their decision. Even a refusal may be tainted by the specific reason that the individual is receiving clinical care. For example, a skin biopsy may be taken during an annual physical may come back negative. The individual may, at that time, refuse to sign a broad consent because he/she does not see any reason to use data excess materials in research. However, several years later the individual may develop an unrelated condition (e.g., diabetes, cancer, etc.). Because of electronic medical records, a researcher may wish to use those data or materials in research related to the second condition. The data or materials can also be de-identified for use in this scenario. If the original broad consent is denied, does that mean that the individual is opposed to their data or materials used for cancer, diabetes or other research? It is impossible to know because, by its very nature, broad consent occurs outside of any

specificity.

Each research project should be viewed independently. If the consent was sought in conjunction with any specific protocol, irrespective of how broad the consent was, this should not represent a prohibition on waiving consent for secondary research.

If an individual was asked to provide such consent, should the absence of a signed secondary use consent be considered a refusal?

No.

Does this prohibition on waiving consent for the secondary use of identifiable private information create a disincentive for institutions to seek broad secondary use consent and instead seek a waiver of consent from an IRB?

Yes.

Under what circumstances, if any, would it be justified to permit an IRB to waive consent even if an individual declined or refused to consent?

Response: If the consent were declined or refused for a specific research project, an IRB must not be able to over-ride the wishes of the individual for that same project. Waiver should be allowable—within IRB discretion—for unrelated projects.

71. Public comment is sought regarding whether particular information security measures should be required for certain types of information or research activities and, if so, what measures and for what types of information or research. Specifically, should the safeguards be calibrated to the sensitivity of the information to be collected?

Response: The data security section of the NPRM is one of the most difficult to respond to because it is so lacking in details. Patient information is already covered by HIPAA security standards, student records are already covered by FERPA. An array of other standards cover financial and various other types of sensitive information. Therefore, it is redundant and unnecessary for the Common Rule to regulate the security systems for these data. As was noted by several responders to the ANPRM, HIPAA standards are too severe and inappropriate for most data not covered by HIPAA. The extensive range and nature of research renders a blanket standard impossible to develop and impose. This is why IRBs review the security and privacy plans in research protocols. Not all aspects of security and privacy protocols can be found in discrete, tiered IT solutions. Any research covered by the exempt or excluded categories should be of such a low risk that there is no need for third party evaluation of security and privacy standards. If this is not possible, then the category of research should be moved to that requiring IRB review (including expedited review). This section should be removed from the final rule unless and until the standards can be fully presented. Until that time, we must evaluate this against the HIPAA security standard which is much too high of a bar for significant portions of an institution's research portfolio.

72. Are the proposed limitations on re-disclosure more or less restrictive than necessary? Are there additional purposes for which re-disclosure of biospecimens or identifiable private information should be permitted?

Response: Re-disclosure should be maintained at the same level and standard as exists in the current rule and does not need to be changed.

73. Will the proposed language at § ll.101(j) be effective in achieving greater harmonization of agency guidance, and if not, how should it be modified?

Response: No. The NPRM language on harmonization is weak and we feel very strongly that it would be completely ineffective in preventing duplication which significantly and unnecessarily increases administrative work. The proposed rule requires nothing other than an agency seeking “consultation.” Even this “consultation” can be waived if an undefined “feasibility” standard is not met. This does not set any standard regarding inconsistency, duplication, or other problems research universities currently encounter. A much more formal process with third party (e.g., Office of Information and Regulatory Affairs) evaluation is needed.

We oppose the proposed revision allowing agencies discretion regarding additional requirements imposed by the conducting or supporting department or agency. This would not “promote harmonization” as suggested, but increase variance in the implementation of the Common Rule. Consistency in the implementation of any revisions to the Common Rule among the 17 Federal agencies signing on will be essential and harmonization with FDA regulations critical.

74. Is mandated single IRB review for all cooperative research a realistic option at this time? Please provide information about the likely costs and benefits to institutions. Will additional resources be necessary to meet this requirement in the short term? Should savings be anticipated in the long run?

Response: No, a mandate is not a realistic option. COGR believes that use of single IRBs for multisite studies can be an effective and efficient mechanism to initiate multicenter protocols in appropriate situations. However, we do not support mandated use and strongly urge OHRP to abandon such a mandate as a component of the Common Rule. Expanding use of a single IRB for multisite studies can be addressed outside of regulations at an agency’s discretion (as demonstrated by the NIH), is currently operationally under-developed by agencies, will not improve human subject protections, and is destined to create a bureaucratic quagmire for investigators and institutions. This provision will not “streamline or reduce burden for IRBs or institutions” as proposed on page 53996 of the NPRM.

We urge HHS to address institutional liability issues and to partner with agencies with an interest in expanding use of single IRB (NIH, in particular) and the research community to assess models which will be successful without the need for a regulatory “stick” to drive the process. If single IRBs are mandated, there will be little incentive for current problems in the system to be resolved because agencies will fall back on the Common Rule requirements and leave institutions to struggle. For the single IRB system to succeed, agencies such as NIH need to better refine their current attempts. We also urge OHRP to define cooperative research such that social and behavioral collaborations do not fall under its aegis and that the number of engaged institutions is far greater than two.

COGR’s member institutions support the concept of relying on a single IRB for many multi-site clinical trials and where appropriate this practice is increasingly adopted. We do not support a mandate for relying on single IRB for studies with two or more sites for a numbers of reasons, as detailed in our letter.

75. What areas of guidance would be needed for institutions to comply with this requirement? Is there something that OHRP could do to address concerns about institutional liability, such as the development of model written agreements?

Response: One key to success is using a limited number of central IRBs. For example, if each institute at

the NIH had its own central IRB in the NCI model, this could be a viable model. However, the high degree of variability by having multiple organizations, public and private, with a mosaic of state laws, and institutional policies, practices, technologies, and cultures, serving as central IRBs creates a problem which cannot be fixed by model agreements. Clarifying the institutional liability issue would certainly facilitate a greater willingness to rely on another institution's IRB. The NPRM noted that OHRP has previously proposed such a change which received widespread support, but it was never implemented for unexplained reasons. Furthermore, it is not clear why the issue of institutional liability needs to be embedded in regulation rather than guidance and practice by regulatory agencies such as OHRP.

76. Would it be useful for this requirement to include criteria that Federal departments or agencies would need to apply in determining whether to make exceptions to the use of a single IRB requirement? If so, what should these criteria be?

Response: As noted above, single IRBs are not appropriate for all multisite research. For example, use of single IRB should not be extended beyond studies where there is an identical protocol implemented at all sites. Single IRB would not be the best model for studies that are designed for collaboration across several institutions with each institution having a discrete role based on local expertise or resources.

Single IRB is also most appropriate when there is a plan to run several protocols through the same IRB. If the single IRB model is not coupled with multiple projects, it will not save time. We also note that applying such a policy to studies with two or more sites would be inefficient. For the purposes of such a policy, 30 or more sites might be more appropriate, though evidence-based criteria should be used in making this determination. Finally, social and behavioral science is not better served by a single IRB review. The genesis of this model is in medical clinical trials and should be restricted primarily to these types of studies, not to minimal risk research.

77. Are the exceptions proposed appropriate and sufficient, or should there be additional exceptions to this mandate for single IRB review than those proposed in the NPRM? If additional exceptions should be included, please provide a justification for each additional exception recommended.

Response: The current exceptions are not adequate, as implementing such a system is extremely complex. Again, we refer you to comments provided to NIH regarding their proposed single IRB policy. We strongly urge OHRP to abandon the single IRB concept as a component of the Common Rule. It is unnecessary, currently operationally under-developed by the agencies, and destined to create a bureaucratic quagmire for investigators and institutions. Instead, we strongly urge you to address institutional liability issues and then to partner with agencies (NIH, in particular) and the research community to evaluate models which will be successful without the need for a regulatory "stick" to drive the process.

78. Is three years appropriate timing to establish compliance with this provision?

Response: Three years is not enough time unless there is a more active partnership between agencies and institutions to establish a model that works and accomplishes the desired outcomes. Imposing this as a regulatory requirement does not encourage or facilitate that partnership. Further, NIH has already proposed a policy that mandates single IRB. If implemented, the proposed compliance delay would be of little consequence.

79. How often should the Secretary's list of minimal risk activities be updated? Should advice be

solicited from outside parties when updating the list?

Response: We support expedited review for studies on the Secretary's list unless the reviewer(s) determine(s) that the study involves more than minimal risk. The NPRM proposes that the list of expedited review categories be re-evaluated at least every 8 years. A summary of ANPRM findings presented to SACHRP suggests that periods ranging from annually to every 5 years were recommended with a mean of 2.9 years. The current list, published in 1998, has never been updated. We agree that regular review, at least every 8 years but optimally 5, makes sense.

The expedited review process should not be limited to the research procedures described on the Secretary's list but rather should be used for any research deemed to be no more than minimal risk by the IRB Chair or designee as suggested in the ANPRM. This would significantly reduce the administrative workload of investigators and institutions without reducing human subject protections and the frequency with which the list was updated would be of less concern.

80. Is this Secretarial list of minimal research activities a useful tool for the research community, or does it represent a loss of IRB flexibility in risk determination?

Response: It is of significant concern that such a list will be viewed by all parties as the definitive and closed list of activities which may be reviewed by the expedited process. It is essential that it not be prescriptive, but provide examples for IRBs. The IRB must still have discretion to determine studies falling outside of the list to be minimal risk.

81. What should IRBs consider when reviewing the plans for returning research results, for example, what ethical, scientific, or clinical concerns?

Response: The nature of the information should be considered if individual research results are to be returned. If the results relate to clinical conditions, then appropriately licensed healthcare professionals should be allowed to return information without restriction.

82. Is the § 11.111(a)(3) and (b) focus on issues related to coercion or undue influence in research with vulnerable populations, and not other considerations related to vulnerability, appropriate? Note that this focus also appears in proposed § 11.107(a).

Response: The populations and considerations as proposed in the NPRM are appropriate.

83. Should pregnant women and those with physical disabilities be included in the category of subpopulations that may be vulnerable to coercion or undue influence?

Response: No. To suggest that pregnancy or a condition that does not affect cognitive capacity are in and of themselves vulnerabilities is insulting. These groups are no more subject to coercion and undue influence than anyone with a specific medical condition or a family history of specific medical problems. At some level everyone is subject to coercion or undue influence unless the research team is ethically engaged in the consent practice.

84. Should populations be considered vulnerable for reasons other than vulnerability to coercion or undue influence? Are the proposed categories appropriate?

Response: Not for the purposes of regulation.

85. Public comment is sought on whether there might be unintended consequences from the clinical trials expansion proposed in the NPRM in § 11.101(a)(2)(i). Unintended consequences may include an

increase in burden or costs, or an inappropriate redistribution of costs.

Response: As we noted in response to the ANPRM, extending the Common Rule to all research, regardless of funding source, at an institution that receives federal funding for non-exempt and non-excluded human subject research (§ 101(a)(1)) will not strengthen human subject protections as suggested in the NPRM. Domestic academic medical centers and institutions of higher education already review all human subject research through an IRB whether or not it is regulated by OHRP or the Food and Drug Administration (FDA). The box is unchecked not to apply a different ethical standard but to avoid those administrative burdens imposed in the current regulations that don't impact the protection of human subjects, such as federal reporting requirements. The proposed regulation will have unintended consequences by increasing the administrative burden on the conduct of minimal risk behavioral and social science research that involve randomization without adding protections to the human subjects involved in these trials and will not impact the organizations that likely cause the greatest concern for the public including private hospitals, clinics, or other health-related entities that do not receive federal funds and conduct clinical trials.

What the proposed expansion would do is require a single IRB for all studies meeting the definition of a clinical trial regardless of the funding source, including minimal risk studies. It stems from the desire for clinical trials to have single IRB review, but doesn't differentiate between medical and behavioral research and would now apply to behavioral and social sciences research as well. This will add significant burden to major research universities as they will likely be designated as the lead institution, but it will not serve to better protect subjects, as the local knowledge, so essential to many social and behavioral research studies, will be lost.

While the costs related to a multi-center trial may potentially be charged to the sponsor, many behavioral studies (e.g., student research, smoking cessation, eating disorders, and other behavioral modification programs) have no funding source and would have to be established and operated at a cost to the institutions. The proposed regulation will increase the administrative burden on both institutions and researchers, create delays in research, increase the costs of research, and potentially discourage some collaborative research. It removes institutions' ability to be flexible with how they apply the regulations without increasing human subject protections. We strongly oppose the proposed expansion. We also recommend that the definition of "clinical trial" should be limited to research studies of "greater than minimal risk" and not include "behavioral health-related outcomes."

86. Public comment is sought as to whether the criterion that the policy extends to all clinical trials conducted at an institution that receives federal support (see the NPRM at § 101(a)(2)(i)) should be further clarified in some way. For example, should it specify a timeframe for support (e.g., within the past number of years), or a minimum monetary threshold value?

Response: This requirement should be eliminated from the revised Common Rule.

87. Public comment is sought on whether the definition of clinical trial (NPRM at § 102(b)) should include additional explanation of what is encompassed by the term behavioral health-related outcomes.

Response: This requirement should be eliminated from the revised Common Rule.

88. Would protection to human subjects in research be enhanced if OHRP conducted routine periodic inspections to ensure that the membership of IRBs designated under FWAs satisfy the requirements of § 107?

Response: OHRP should use a risk-based approach if considering inspections. Institutions currently inspected by the FDA should be eliminated because deficiencies in IRB membership would be a matter of public record. Institutions that have elected to undergo voluntary accreditation should be excluded because of having had a rigorous third party review. The remaining subset of organizations should then be evaluated based on the volume and nature of their research in selecting sites to visit.