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Office of Clinical Research and Bioethics Policy
Office of Science Policy, NIH
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Bethesda, MD 20892

Comment on the NPRM and the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

We write on behalf of the University of Michigan Office of Research and the Medical School to comment on the National Institute of Health's Notice of Proposed Rulemaking as published at 79 Federal Register 225 (November 21, 2014), as well as the proposed policy changes promulgated as the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.

The University of Michigan's research portfolio exceeds eight hundred million dollars per year in federally sponsored programs, of which more than two thirds comes from the National Institutes of Health. Clinical research conducted at the University of Michigan is responsible for important scientific advances in a variety of fields, and it includes a large number of clinical trials that are conducted to evaluate new drugs, new biologic agents, new devices, and new strategies for the treatment and prevention of disease.

Our response consists of four parts:

I) Comments on specific provisions of the NIH NPRM document
   A. Items for which the agency requested input
   B. Specific regulatory provisions and discussion of their impact
II) Comments on the NIH Draft Policy
III) Additional suggestions for and general comments on ClinicalTrials.gov
IV) Concluding remarks

Part I. Comments on Notice of Proposed Rule Making Document

Topics Discussed in the Overview, including those on which comments are invited, but for which there are no draft regulatory provisions per se.

1. Submission of Non-Technical and Technical Summaries of Trial Results
"If non-technical or technical narrative summaries can be consistently produced without being misleading or promotional, patients, members of the general public, clinicians and researchers might benefit from brief, well-written, accurate, and objective summaries of the results of individual clinical trials"…. "Another question to be addressed is whether a single, brief summary

of an individual clinical trial can provide sufficient background or context to avoid being potentially misleading to a clinician or patient interested in the clinical significance of the results…Accordingly, NIH plans to undertake an evaluation to assess… whether [such summaries] can be provided in a manner that is objective and not misleading… We invite further public comment on **methods that we might employ** to help answer this question so that we can explore this issue more thoroughly before making a final determination." (emphasis added) FR 69581 col.23 (#6)

Possible Methods. As to how to determine whether narrative summaries could work, perhaps a test site could be funded through a request for proposals mechanism to evaluate summaries from a random sample of different types of trials. Different constituent sources could create the summaries – and then volunteers could be recruited to read and respond to survey questions about the summaries. Science educators and disease support networks might be particularly interested in participating in such an experiment to see if the lay public finds such summaries useful and can understand them. Such a process would probably be a multi-year endeavor requiring a significant amount of funding, but, if done properly, it could shed light on which current parts of ClinicalTrials.gov can be understood by different sectors of the public.

There are many potential challenges and pitfalls in the process of providing non-technical and technical summaries of trial results. First, there is the question of who would provide those summaries. From one perspective, the investigators themselves would logically be in the best position to interpret the results and summarize them, as they are the most familiar with the data, the protocol, and the context of the trial. However, the International Committee of Medical Journal Editors guidelines allow journals to treat textual passages beyond 500 words as "prior publication", which would be grounds for rejecting a proposed article on a trial (http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/). Thus, academic researchers (or others) might either be prevented from writing truly effective summaries of more complex trials in ClinicalTrials.gov or forfeit the ability to publish a longer, more comprehensive piece later in a high quality journal. Additionally, it can be challenging for scientists to put their findings into non-technical language, just as there remain huge difficulties with informed consent documents conforming to regulatory requirements for ease of understanding. But even without these concerns, would writing such summaries be a better use of our scientific researchers' time than beginning the next research project?

Is this a role the government itself could take on? Is there any other cadre of writers or junior scientists who could be enlisted to digest the protocol and results to draft such summaries? If so, what opportunities would the researchers or trialists have to discuss, dispute, or reply to such summaries?

Recommendation: We support the continued deferral of any requirement for technical or non-technical summaries. One option we would not oppose would be to create fields, which would allow for technical or non-technical summaries to be added on a voluntary basis. Such a

pilot project, possibly limited to a small number of studies, could be more easily vetted by the ClinicalTrials.gov staff to avoid anything promotional or misleading and then used as a "testing ground" with citizen volunteers and commenters to determine if this is a useful or effective option.

1. **Submission of full protocols**
   "We invite public comment on whether the registration and results information that is proposed for submission in this NPRM is sufficient to meet the statutory requirement …to provide 'information on the protocol' as may be necessary to help evaluate the results of the clinical trial or whether submission of additional information, **including submission of the full protocol should be required."** FR 69582 col. 2 (#7)

   We believe that the proposed registration elements meet the statutory requirement. Even if it is subsequently found that additional details might be needed, we believe that these needs would be better addressed by including some additional data elements extracted from protocols than by requesting actual copies of full protocols. If full protocols were to be required, both proprietary and intellectual property interests could be at risk. Redaction is time-consuming and often not perfectly done. Further, standards for submitting amended protocols and revisions would need to be established, creating an even greater burden on investigators conducting clinical trials as Responsible Parties. The tens of millions of additional pages of non-standardized, partially redacted, and overlapping protocol versions with amendments applying at different points in time during a trial would be more likely to cause confusion than clarity at the expense of significant time and effort, and at the risk of proprietary information slipping through redaction efforts inadvertently.

   Recommendation: We believe that full protocol submission would complicate public access to data rather than improve it. The current information detailed by registration and results summary submission of data elements for clinical trials should remain sufficient to meet compliance standards for public sharing.

2. **Increasing the Time Period for Submitting Results Information to 18 months**
   "The public comments on this matter helped inform our view…We …have decided not to propose lengthening the deadline for submitting results information, but to propose specific mechanisms for accommodating extended data collection for secondary outcomes to avoiding [sic] the premature unblinding of trials." FR 69582 col 3 (#8)

   The Food and Drug Administration Amendments Act specifically allows for the regulations to extend the time period for submitting results information to 18 months, even as it allows for the expansion of the results reporting requirement to include results for Applicable Clinical Trials that are of drugs and devices not approved by the FDA.

The comments on which the NPRM based this decision were shared by mostly pharmaceutical companies in 2009, at a time when very few other parties had significant experience with the extent of the work involved in posting results information. Indeed, in the years since 2009, the federal estimates of results reporting work have increased from 25 hours, to 40 hours, to the present estimate of 50 hours. (79 FR No. 225 p. 69664 (initial and updates) compared to Federal Register / Vol. 77, No. 27 / Thursday, February 9, 2012 /p. 6808). **So it seems more than reasonable that with a doubling of the work expected, a statutorily pre-sanctioned expansion of time frame from 12 to 18 months would be sensible.** We request this further because the NPRM recognizes a number of commercial reasons for additional extensions of time for reporting, related to possible applications for FDA approval – such as the two year delay (69633), but these relate exclusively to commercial pharmaceutical or device interests and do not show any recognition of the complex and competing obligations upon academic medical researchers, who often have teaching and/or clinical responsibilities in addition to their clinical research roles. Sabbaticals, service (clinical care, education) obligations, participation on scientific review boards for journals, as well as for NIH and other governmental agencies, all compete for researcher time to organize, analyze, format, and report results.

Most importantly, the researcher's stock in trade is the published, peer-reviewed article. Given the many advances to medical practice and translational medical innovation begun by university researchers, it would be appropriate for the government to show comparable deference to academic researcher interests as it does to commercial interests. One way to do that would be to allow pre-publication delays for up to two years, just as the NPRM proposes be allowed for pre-FDA approval delays.

Barring such an approach, a simpler response would be to at least extend the standard reporting time to 18 months. The NPRM commentary itself notes on FR 69585 Col. 3 that "For the great majority of clinical trials, no publications are available for comparison at the time results are submitted to the data bank." This would not be fully solved, but would be partially addressed, by extending the time required to post results in ClinicalTrials.gov, with the added advantage of the prior "quality control" provided by the journals' peer review process.

Several articles have been published in recent months and years claiming that academic medical centers are less efficient in reporting results than the drug and device industries. Yet, none of them have seriously considered the legitimate reasons why this might be the case: Industry has the capacity to assign multiple people to the same tasks in an intentional redundancy. It has budgets that greatly exceed academic resources, because it can generate massive profits. And its personnel do not have the same extent of competing tasks – all directed toward promoting public health – that academic medical researchers have. It behooves the government, wishing to promote the investigative and discovery-oriented spirit among academics, to support and encourage rather than to shackle scientists with these broad obligations.

A six month extension of the time to report results from the current 12 months to 18 months would have minimal negative impact on the speed of scientific progress, but would allow multi-tasking researcher-physicians to better prioritize their time and effort while remaining compliant.

Recommendation: We recommend that the proposed rule be modified in §11.44 (a) to allow 18 months (rather than 1 year) after the primary completion date to report results, and that the NIH consider creating other standardized exceptions or delays for those trials for which a plan of publication is in process.

3. **Standard Data Formats.** "We have developed a mechanism for uploading results data in an automated electronic fashion using eXtensible Markup Language (XML) files. We do not believe that uploads of data tables in other formats will allow for the comparability and consistency desired across trials and do not include such a mechanism in our proposal." FR 96583 col 3-96584 col. 1 (#10)

   Request: Physicians and research teams are rarely familiar with XML uploads. In addition, many academic medical centers do not have a single database that is used institution-wide, which makes developing XML upload procedures difficult. For example, Excel, Access, and REDCap are often used for data collection. Both Access and REDCap can be exported to Excel. The recently released, user friendly Excel upload currently provided by ClinicalTrials.gov for AE reporting has been enthusiastically embraced by our research community and has reduced the need for manual entry. Please confirm that the Excel upload of adverse events will still be supported.

4. **Quality control procedures and updating previously submitted clinical trial information.** Consistent with the proposal in § 11.66 regarding correction of clinical trial information, responsible parties would be required to correct errors, deficiencies, and/or inconsistencies not later than 15 calendar days after being informed of them by the Agency or otherwise becoming aware of them (e.g., if they discover the errors, inconsistencies, and/or deficiencies themselves), whichever is later. FR 96584 (#12)

   Proposed § 11.64(b) identifies several data elements that must be updated not later than 30 days after a change occurs (e.g., Overall Recruitment Status and Availability of Expanded Access), requires updates to U.S. FDA Approval, Licensure, or Clearance Status not later than 15 calendar days after the change occurred, and specifies that if a protocol is amended in such a manner that changes are communicated to participants in the clinical trial, updates to relevant clinical trial information must be submitted no later than 30 calendar days after the protocol amendment is approved by the human subjects protection review board. FR 96587 (#13)

   A mixture of 30-day and 15-day windows increases the complexity of understanding and complying with reporting and updating requirements. In addition to complexity posed by

having windows of various duration, a 15-day window to correct errors will be more burdensome for investigators than a 30-day window. Particularly in cases where the changes are complex, this would not allow sufficient time to produce additional statistical recalculations, if necessary, or complete any required internal review and approval processes. It bears noting that academic medical researchers periodically have to accommodate their schedules to periodic stretches of intense clinical obligation, which can encompass an entire 15-day period.

Recommendation: A uniform 30-day standard window for all short-term deadlines should be adopted. Shorter windows do not provide sufficient increased benefit to information seekers relative to the increased compliance burden and risk.

5. **Adverse events classification.** "We propose to require responsible parties to use the organ system classes specified in the Medical Dictionary for Regulatory Affairs (MedDRA). We also propose to require responsible parties to submit the total number of participants affected by an adverse event at the organ system level. This information would be required for each arm of the clinical trial and for each adverse event table." FR 69589, col 3, FR 59590.

   Academic medical centers, other than Cancer Centers, have little familiarity with this classification system. Further, to the extent that increasing numbers of trials will be entered that do not test drugs or devices at all, this highly medical-centric approach may be particularly inappropriate and unfamiliar to behavioral and other researchers.

   Recommendation: We recommend that the Agency forego this choice and keep the classification of adverse events as simple as possible, consistent with current practice.

6. **All-cause mortality information:** FR 69590 col. 3

   Recommendation: We do not support the addition of an all-cause mortality table, unless it is accompanied by additional explanatory fields that allow for attribution and connection to other causes. However, if these fields were added, the risk of re-identification of individual trial participants would increase -- which could, in turn, require more waivers of results reporting.

7. **Standard Vocabulary for Adverse Event Terms** FR69590 col. 3

   Recommendation: We request confirmation that MedDRA coding continue to not be required, as it would pose an enormous burden for academic medical centers to develop an infrastructure to support this coding while providing little public benefit.

8. **Privacy Considerations**: We appreciate your acknowledgement that small trials with unusual populations or disease conditions may require waivers of data reporting out of concern for re-identification risks. FR 69591 col. 3

9. **Results information.** "The Agency proposes to exercise its authority under § 402(j)(3)(D)(iv)(II) of the PHS Act in situations when partial results are due on or after the effective date of the rule to require the responsible party to submit clinical trial results information under proposed § 11.48 for all outcome measures, including primary outcome measures submitted prior to the effective date of the rule." FR 69593 col. 3

   Updating previously approved outcome measures that have passed NIH/PRS quality review will present a significant burden for investigators. Attempting to comply, or explaining to PRS why compliance is not possible, will be very time-consuming for investigators, PRS administrators at the institution, and PRS reviewers. ClinicalTrials.gov is likely to continue to be an evolving system, in which later trials may have more complete, or more easily understandable, results reporting. Such improvements should be welcomed and appreciated, but each such progression should not be a cause for previously completed work to be required to be revised. Investigators and PRS administrators should be able to move forward with newly completed trials, without being encumbered by the re-work of applying new compliance standards to old work.

   Recommendation: We recommend that the Agency forego this choice and make §11.48 results reporting requirements apply only to those outcome measures that have not yet been submitted.

10. **Requesting a good-cause extension of the results submission deadline. "**The following non-exhaustive list enumerates scenarios that we generally do not believe ordinarily would constitute good cause: Pending publication…We invite public comment on these specific situations and on more general criteria that could be used to determine what constitutes good cause for an extension." FR 69637 col. 1

    The concern that results reporting would be prior publication is not the only reason that a researcher might want to have his article drafted and accepted for publication prior to posting results in ClinicalTrials.gov. Specifically, the process of drafting and producing an article may be far more collaborative, and therefore create far more reliable data and analysis, than a single responsible party in isolation trying to enter the data into ClinicalTrials.gov format. The pre-publication process, involving iterative drafting with other researchers, surviving peer review, and so forth, is designed to improve the quality of the data and the accuracy of its interpretations.

    Further, as long as the entire academic medical research system still relies on peer-reviewed publications as the gold standard of academic achievement, and since that also serves the public interest in making information (with interpretation) available to the public, it would be as appropriate to grant extensions for work on an article going to press as it is to give the pharmaceutical and device industry extensions for study articles that they intend to take forward to FDA application. In each case, NLM would be honoring and furthering the principal drivers of that sector of our economy and science discovery. This sort of collaborative recognition of "what

makes researchers tick" would spur more enthusiastic compliance with the regulations than punitive threats of posting names of late responders.

Finally, there may be some types of analyses that inherently take weeks or months after last patient data collection before they can be begun. For example, if core facilities are needed for certain types of genomic analysis, and they have a substantial backlog in demand, a researcher may not have all of the necessary data in hand for preparing the results reporting until some time later.

Recommendation: Extensions of results reporting should be granted for reasons that keep researchers doing their work diligently and well, including consideration of whether the quality of the data will be improved by granting the extension, either because the peer review process may improve the resulting accuracy or because specialized analyses or services may take unusually long times to complete.

A. Specific provisions of the proposed rule – and their discussions

1. 42 CFR § 11.4 (c)(3)

Withdrawal of the designation of a principal investigator as the responsible party. "(i) In the event a principal investigator who has been designated the responsible party becomes unable to meet all the requirements for being so designated under paragraph (c)(2)(i) of this section, the principal investigator must withdraw the designation in the form and manner specified at http://prsinfo.clinicaltrials.gov, at which time the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section.
(ii) In the event a principal investigator who has been designated the responsible party is unable because of death or incapacity to withdraw his or her designation, the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section." Federal Register 69667 col. 2

Responsible Party and Sponsor roles differ between large corporate trials and the autonomous scholarship of academic researchers; universities cannot control data as tightly as centrally run corporations. Large corporate managed and funded trials are genuinely different from smaller scale investigator-initiated clinical trials. Such smaller scale trials are very rarely abandoned by the principal investigator, but in those rare circumstances (death, disability or transfer to another institution or career), there is not always another co-investigator who can take up that trial and continue it. In these circumstances, when there is no appropriate replacement investigator, the institutional sponsor should be able to submit a waiver of results requirement. This would allow for the record to be closed from the institutional account and posted on the public site with a notice of the reason that the study was terminated and only partial

results (if any) were obtained. It would be helpful to have clearer means of noting such trials as "closed", both for the institutional account and on the public-facing side, so that everyone understands that this is all the data that will ever be available. We have spoken with peer institution PRS administrators who have had the experience of trying to complete results for studies that were terminated due to death or inaccessibility of investigators. There was no efficient mechanism to remove the problem records from the institutional account. These situations use inordinate amounts of institutional resources, attempting to locate abandoned data and composing language that satisfies PRS reviewers. Considerable PRS reviewers' time is also spent shepherding investigators and academic medical center PRS administrators through the process. In the end, the posted information often does not provide commensurate benefit to the public or the scientific community.

Recommendation: We recommend that subsection (ii) be rewritten to add a second sentence: (ii) In the event that a principal investigator who has been designated the responsible party is unable because of death or incapacity to withdraw his or her designation, the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section. **If the sponsor cannot identify a new, appropriate designee, it may request a waiver of results reporting in accordance with § 11.54.** We also recommend that in both of the subsections i) and ii) above, the word "that" be added after "event", for ease and clarity of understanding.

2. **§11.10, Definitions Applied** – "(a) …***Adverse Event*** means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research." Federal Register 69667 col. 2

   The required terminology for Adverse Event is vague and unclear, and the scope of the definition utilized is unnecessarily loosely defined. Regulatory definitions of "adverse event" differ from each other and from IRB definitions. Further, **it would be most helpful to confirm that the definition does not create a new, implied requirement that all trials record all adverse events, but rather reaffirms current policy that all adverse events which were recorded according to the protocol would be reported in ClinicalTrials.gov.** While this may be implied by the language of the NPRM (69587) that: "Proposed §11.64(a) (2) specifies that a Responsible Party must submit updates until the final clinical trial results information has been submitted for all primary and secondary outcome measures and all adverse events **collected in accordance with the protocol**" (emphasis added), it bears noting that adverse event data in ClinicalTrials.gov may therefore be inconsistent in how comprehensive it is, because some protocols will require data collection in different ways than others.

   Recommendation: We recommend that "adverse event" be explicitly defined in a manner consistent with current requirements stipulated by IRB reporting at continuing review. One

approach would be to define "adverse event" as §11.10 currently does, but add the following sentence, "Notwithstanding this definition, only those adverse events (and serious adverse events) that are required to be recorded according to the protocol and meet the results reporting thresholds specified in §11.48 (a)(4) are required to be reported."

3. **§ 11.10 "*Completion date*** means, for a clinical trial, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for all of the primary outcomes." (FR 69668 col. 1)

   Recommendation 1: We strongly support retaining use of the term "Primary Completion Date" since the concept that a study is "Completed" but can still be "Active, not recruiting" seems mutually exclusive, and a clear definition of "Primary Completion Date" could fulfill the same purpose. A PRS-specific definition of simply "Completion Date" may cause confusion and lead to posting of inadvertently incorrect information. "Primary Completion Date" is recognizable to current users of the system and is a term whose definition is less likely to be "assumed" and misinterpreted by experienced and inexperienced PRS users.

   A problem remains for cases where a study is terminated early: Take the case where a decision is made to terminate a study at a point more than one year after the last previously enrolled subject reached the data collection point for a primary outcome measure. At the point of enrollment closure, as the current definition appears to be written, the Responsible Party is already non-compliant with results reporting requirements, even though the study was open for enrollment and actively screening subjects. Because of the high penalties for late results entry, a clarification of this definition is needed to avoid the unintentional noncompliance caused by a change in circumstance or a stalling in enrollment. This can be solved by adding a second sentence after the first: In the case of studies that are terminated before enrollment goals were reached, the primary completion date is the later of a) the date of the decision to terminate the study or b) the date that the last data was collected for a primary outcome measure.

   Recommendation 2: We appreciate and endorse the clarification that for clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for **all** of the primary outcomes. This is a truly helpful enhancement to efficiency.

4. **§ 11.10 "*Interventional*** means, with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according to a protocol to **evaluate the effect of the intervention(s)** on biomedical or health related outcomes." FR 69668 col. 2 (emphasis added)

This definition, with its assignment and causal connection intact as dual additive requirements, would exclude certain kinds of trials, which nonetheless would be classified by the "algorithm" created by responses to questions in the ClinicalTrials.gov registration system as meeting the test for interventional. Example: A trial in which participants are assigned to receive a drug, or use a device, not to measure its effects on biomedical or health outcomes, but to create a background condition, for example, noisy distraction, or a drowsy sensation, which allows something *else* to be measured more effectively, would not be an "applicable clinical trial" following the definition above. However, for that result to be obtained with a flow-chart or algorithm question, the question has to be, "Does the trial study a drug or device?" with a confirmation that "study" means "look at the effects of" rather than "Does the trial use or assign people to a drug or device?", which would make such a study appear to become an Applicable Clinical Trial.

Recommendation: This is one of several definitions that point to the need for an appeals process for the determination of Applicable Clinical Trials (ACT) created by the algorithm of using data elements to determine if a study meets the definitions of an ACT.

5. **§ 11.10 "*Outcome measure*** means a pre-specified measurement that will be used to determine the effect of experimental variables on the human subjects in a clinical trial. See also primary outcome measure and secondary outcome measure." FR 69668 col. 3

   Recommendation: We strongly encourage the NIH to provide additional resources and training to help investigators understand the particular structure and specificity required for the statement of Outcome Measures. This section triggers the most PRS Quality Assurance (QA) questions and comments of any in the registration process, and it presents a significant burden to PRS Administrators attempting to assist investigators to register, respond to QA comments, and report results. Indeed, it has been our experience that PRS staff members have more uniform understandings of these concepts than researchers do. Moreover, should the proposed NIH draft policy go into effect as written, many of the behavioral trials that will be newly required to report results may not have outcomes which fit the quantitative "units of measure" model currently expected. It is not necessarily realistic or "transparent" to assume that all "outcomes" are quantifiable in this way. Some research, especially in early and exploratory phases, may look for health outcomes that are best characterized descriptively or qualitatively. Trying to fit not only square, but also star-shaped, pegs into round holes may constrain, rather than support, rapid scientific advancement.

6. **§ 11.10 "*Study Start Date*** means the estimated date on which the clinical trial will be open to enrollment of human subjects. If the clinical trial has enrolled the first human subject, the actual date on which the first human subject was enrolled." (16) FR 69669 col. 3

   Recommendation: The University of Michigan recommends that ClinicalTrials.gov call this field "Date of First Enrolled Participant", instead of "Study Start (anticipated and actual)". For other purposes, such as human subjects protection, IRBs consider studies to have "started" when

they are IRB-approved and recruiting, regardless of whether any participants have yet enrolled. The inconsistency among definitions of the proposed term will confuse many parties more than it will help researchers comply.

7. **§11.10 "*Facility Information*** means, for each participating facility in a clinical trial, the following information: (i) Facility Name, (ii) Facility Location and (iii) Either: (A) For each facility participating in a clinical trial, Facility Contact, including the name or title, telephone number, and email address of a person to whom questions concerning the trial and enrollment at that site can be addressed or (B) Central Contact Person, including the name or title, toll-free phone number and email address of a person to whom questions concerning enrollment at any location of the trial can be addressed." (32) FR 69670 col. 2

   Recommendation: We recognize the importance of providing contact information to interested research participants. Our interpretation of this section of the proposed rule is that facility name and contact information can be provided with a central contact person and toll-free phone number for the entire trial. Based on the comments provided by other parties, we believe it would be helpful to make that clearer, perhaps by saying, "Central Contact Person for the entire trial".

8. **§11.10 "*Record Verification Date*** means the date upon which the responsible party last verified the entire clinical trial information in the entire ClinicalTrials.gov records for the clinical trial, even if no additional or updated information was submitted at that time." FR 69670 col. 3 (37)

   Recommendation: We request the removal of both instances of the words "entire". The implication that each time a Responsible Party reviews the record, he or she will have reviewed every single data element is unrealistic and would, in and of itself, expand the time required for compliance.

9. **§11.10 "*Responsible Party Contact Information*** means administrative information to identify and allow communication with the Responsible Party by telephone, email, and regular mail or delivery service – includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the Responsible Party or a designated employee of the organization that is the Responsible Party." 38 FR 69670 col 3

   It is our understanding that the level of detail proposed for requiring contact information is for agency use only. The contact information already required and posted for ClinicalTrials.gov should remain adequate.

   Recommendation: We request that the additional administrative information at this detailed level not be required, as this information should already be available and on file with the NIH and FDA. If required, however, we request confirmation that this additional Responsible Party contact information not be made publicly available.

10. §11.28(c) "***Expanded Access Record.*** If expanded access is available under Section 561 of the Federal Food, Drug, and Cosmetic Act to a drug studied in an applicable drug clinical trial and specified data elements have not been submitted for a previously-registered applicable clinical trial of the drug, the Responsible Party must submit the clinical trial information in the form of an expanded access record." FR 69672 col 3

    Will this proposed requirement apply *only* to responsible parties (sponsor-investigators) who hold or manage both Expanded Access (EA) and non-EA trials using the same drug? If not, then such a requirement is problematic for investigators conducting research at academic medical centers in which they are IND holders for one set of investigational purposes but do not control expanded access to that drug. They may be IND holders for a particular purpose, but they may not even have personal knowledge of whether Expanded Access is available for this drug for the same or for a different purpose. Unless the FDA requires manufacturers to notify all investigators pursuing studies about a particular drug when any EA becomes available, this is an impossible obligation. Even if manufacturers were to notify all clinical investigators using their product, if there are multiple investigators, then which responsible party would be responsible for the expanded access record? It would make more sense for the responsibility for expanded access records to rest with the manufacturer who controls the drug or device.

    Recommendation: We request revision and simplification of this provision such that manufacturers who control investigational products have the responsibility to post expanded access records, unless another party specifically holds the expanded access IND, in which case that party would be the responsible party for the expanded access record. Further, we request that if records of trials studying drugs that have expanded access availability are to be linked to those expanded access records, it should be ClinicalTrials.gov that posts those links with appropriate caveats that they may or may not be for the same clinical indications, purposes, or populations.

11. ***§11.48(a)(3)(v) "Statistical Analyses.*** Result(s) of scientifically appropriate statistical analyses, if any, including any statistical analysis that is (A) pre-specified in the protocol and/or statistical analysis plan that was performed on the outcome measure data, (B) made public by the Sponsor or Responsible Party prior to the date on which results information is submitted for all primary and secondary outcome measures in the clinical trial, **or** (C) conducted in response to a request made by the U.S. Food and Drug Administration prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial." FR 69638, 69676 col. 1 emphasis added.

    It is unclear whether this will require the reporting of all statistical analyses done for a clinical trial. If each statistical analysis that is ultimately completed is required to be reported, this would be excessively burdensome to the Responsible Party, without any significant added benefit to the lay public or in the interest of data sharing. Further, NPRM (69608) states that secondary outcome measures are considered "to be those outcome measures (other than primary outcome

measures) that are not considered exploratory and for which there is a specific analysis plan". Based on the information in IV.C.4, §11.48 (a)(3)(v) (discussed at FR 69642) for Statistical Analyses, results summary reporting would be required for secondary outcome measures if they are pre-specified in the protocol. The NPRM further states the view that "outcome measures that are not part of an analysis plan or are indicated to be exploratory as tertiary or lower level outcome measures that do not need to be submitted to ClinicalTrials.gov, but for which information may be submitted voluntarily".

Academic research frequently includes exploratory outcome measures. These outcome measures may or may not be identified in the protocol.

Recommendation: We request clarification and confirmation that the presence of an analysis plan in the protocol (as asserted by 'A' above) does not change the exploratory nature of an outcome measure and therefore statistical analysis results for the exploratory outcome measure should not be required to be reported in ClinicalTrials.gov.

12. **§11.35 and 11.52 When will NIH post submitted information (for registration and results)?** Both of these sections and their relevant discussion in the preamble (FR 69631 and 69646) discuss an intent by NIH to publish registration or results information within 30 days whether it has fully completed the PRS QA process or not with an indication that it has not completed that process if it hasn't.

    The NPRM discussion noted that there are times when Responsible Parties let registrations or results reports lag between the time that PRS QA is performed and the necessary changes are made. We appreciate that this can be frustrating and that the National Library of Medicine is eager to get information shared. If other incentives (positive or negative) are needed to encourage Responsible Parties to be timely in their reporting or their responsiveness to PRS QA concerns, the final approved version could be designated with a symbol showing that that Responsible Party was timely or tardy. However, in this era of "click and grab" information sharing, it is genuinely irresponsible to post data on a government website that has not fully met the government's minimal standards for Quality Assurance. The notice that the information has not yet passed Quality Assurance could be easily overlooked or ignored, and journalists or lay persons could spread misinformation far and wide before the government or Responsible Party had sufficient opportunity to make the correction. Undoubtedly, there will be other occasions when data in ClinicalTrials.gov is misinterpreted, miscopied, or in some other way misused with harmful result, but this is one case where a little government patience, tolerance, and ingenuity can prevent considerable potential damage.

    Recommendation: Please do not post information of any sort that the government believes to be inaccurate or misleading, or simply inadequately clear. We cannot overstate the importance of amending these two sections of the regulation to avoid the risks inherent in them.

13. **§11.64 Updates to Clinical Trial Information Submitted to ClinicalTrials.gov.** "a)(1) not less than once every twelve months…(3) A responsible party must continue to submit updates as specified in this section until the date on which complete clinical trial results information specified in §11.48 has been submitted for all primary and secondary outcomes and all adverse events that were collected in accordance with the protocol." FR69679 col. 1 and 2 and ***(b) Items Requiring More Rapid Updates*** FR 69679 col. 2

    While we understand the concern to ensure the accuracy of the study information within ClinicalTrials.gov in a timely manner, the mixture of 15 and 30 day requirements outlined by the NPRM is confusing at best. Further, because some of the data elements which trigger these updates may not be disseminated directly to the researcher (e.g., § 11.64(2) U.S. FDA Approval, and §11.64(3)(b)(1)(iii) Intervention name change and establishment of non-proprietary name), but instead would be sent to a manufacturer who may or may not maintain regular contact with the researcher serving as a Responsible Party, there may be a significant time lag before the academic sponsor-investigator has any reason to know of these changes, much less time to enter them into the system.

    More generally, the updates currently in place in the PRS system are largely based on six month structures, which are significantly more stringent than the requirements for updating the IRB and do not correspond with the current requirements for annual updates (in the majority of human subjects research) for continuing review and approval of human research studies. Annual updates for all non-urgent matters would allow researchers and institutions to align ClinicalTrials.gov updates with IRB renewal updates, making for a more efficient and less error-prone system.

    Finally, we note that the current system has no clear means for the Responsible Party to indicate, for PRS administrative awareness, or for public understanding, when a record has had all the data in it that s/he can reasonably expect to ever enter. Whether a Responsible Party is retiring, or a trial was successfully completed with much data entered, or an observational study was registered simply to publicize it, there should be a simple way for the Responsible Party (or his or her institution if necessary) to indicate that a record is complete and will have no more data entered into it later.

    Recommendation: We request streamlining to two sets of timeframes: 30 days for urgent matters and annual updates for everything else. These are sanctioned in the statute and can be more readily implemented by institutions and researchers in an efficient and compliant manner.

II. NIH Draft Policy on Clinical Trials Registration and Results Reporting.

Investigators conducting independent research at academic medical centers will be severely impacted by the policy as currently proposed, and investigator-initiated clinical trials will be

discouraged by the onerous requirements without any corresponding gain. Our comments on the NIH Policy are summarized with certain key points enumerated below:

While we appreciate and support the policy's intent to "support[s] the NIH mission to advance the translation of research results into knowledge, products, and procedures that improve human health", we do not see strong evidence put forth to show that this policy would, in fact, support that mission more efficiently or effectively than maintaining the set of "encouragements" to register and report that is currently in place, or than simply requiring that all NIH supported clinical trials register in ClinicalTrials.gov but not necessarily be required to post results.

No cost benefit analysis has been put forth to justify the draft policy.
The problem is smaller than it seems. The statement that "less than half of NIH-funded clinical trials had been published within 30 months of trial completion" is quoted in the background section of the proposed policy as justification for this policy originates from Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross-sectional analysis. BMJ. 2012; 344:d7292. This article has been used to raise alarm bells about transparency, but the very same article, when read in full, belies the core "alarm". It noted that "Trials completed in either 2007 or 2008 were more likely to be published within 30 months of study completion compared with trials completed before 2007."

The world of public information-sharing has expanded enormously since that time, and even the article shows the more positive trend that "54% of NIH supported trials completed in 2007 or 2008 were published in less than 30 months." (emphasis added) The article also noted that "after a median of 51 months after study completion… a third of NIH funded trials remained unpublished" meaning that two thirds were published with no NIH policy requirement! Thus, a "solution" is being proposed which will require an average of 50 or more hours work (FR p. 69663) for every NIH funded study but which, in fact, is only "needed" for less than one third of NIH funded studies.

The solution could be worse than the problem. At the very least, before imposing such a requirement, ought there not be a follow up analysis performed to see if those publication numbers have continued to improve as the article suggested they were beginning to do? If they have, and the trend is in the right direction, why implement a policy when voluntary behavior is already improving? Indeed, such a move could actually be counterproductive by distracting researchers from issues that more directly affect human safety, data integrity, and rapid advancement of scientific discovery.

The policy may actually discourage some health research. Innovative investigators who spend hundreds of hours pursuing scientific discovery, even while they may be providing urgent clinical care, are neither inspired nor invigorated by requirements to shape all data into the same size boxes. Even if others are hired to do some of that data entry, the researchers are still held

responsible. Further, only those institutions that are large enough to support a solid infrastructure will be able to continue to seek these funds. How many inventions and discoveries will be lost because scientists can no longer keep up with the demands of ever-increasing unfunded federal mandates?

Early publication of some studies' data may be more misleading than helpful. It bears noting that many pilot studies funded by NIH are intentionally designed to be small in order to engage in discovery that will help design better subsequent studies or trials, with sufficient power to be meaningful and reliable. So some portion of the one third of trials referred to in the Ross article which were not published within 4 years, might nonetheless have been the pilots or foundational trials for larger trials that are or will be published soon after their completion. Requiring the results data from such pilots to be in ClinicalTrials.gov might confound rather than enhance public understanding, and would certainly divert energy which could otherwise go more directly toward the larger, more material studies.

Similarly, for those studies that are unable to enroll sufficient numbers to support the statistical design, reporting those (underpowered) results will not add much to scientific knowledge and could be potentially misleading. Even NIH sometimes decides that trials or studies are not able to justify further investment in them in a particular form (e.g. National Children's Study, as announced by Francis Collins Dec. 12, 2014, and reported in http://www.nature.com/news/nih-ends-longitudinal-children-s-study-1.16556). When trials do not come close to achieving their original goals, given that contact information is already available in the ClinicalTrials.gov database, wouldn't registration alone be sufficient to allow those who are truly interested to find out more if they need to? There is already a multiplicity of requirements for detailed data sharing from NIH and within the scientific community. Is the ClinicalTrials.gov level of "formatted high level data" really a one-size-fits-all solution that will be efficient an efficient way to improve scientific discovery?

The draft policy potentially undermines human subject privacy. Note, although it is not mentioned in the NIH Draft policy, one would hope that the NIH policy would allow for waivers of results reporting in cases where circumstances may pose a risk to human subject privacy. Even the NPRM commentary suggests that privacy concerns might be an acceptable reason for the waiver of results reporting. Since, for many NIH pilot studies, sample size may be as small as 20, then the 5% threshold for adverse event reporting is in fact posting individual level data, which given geographic identification, might be quite easily re-identified.

Other NIH policies already accomplish most of this goal. Other NIH policies already require more effective and complete data sharing among members of the scientific community who can most effectively leverage that data to future advances in science and medicine. The Public Access policy requires all NIH funded published literature to be freely available to the public in a reasonable time frame. A more cost effective means to achieve nearly the same goal as this draft policy would be to simply require all NIH supported human subjects research to register in ClinicalTrials.gov and link to the published articles (given that those are already required to be

Freely available via PubMed Central). By so doing, NIH would acknowledge the value of peer-reviewed publications, and not ask professors nationwide to engage in the rework necessary to wedge the data into ClinicalTrials.gov formats. When an NIH staff person was asked about this duplication of effort, s/he responded that not all articles are written for the lay public. This argument is somewhat ironic given that a 16 year old's access to articles is used as a primary justification for the Public Access requirement. S/he also suggested that articles "tell a story" and ClinicalTrials.gov just shares the results neutrally. But if the point is that publication is secondary to the importance of posting "neutral" results in ClinicalTrials.gov, then the purported low publication rates which are touted as a reason to require ClinicalTrials.gov sharing would be irrelevant. The two arguments are inconsistent.

Clinicaltrials.gov data is not inherently purer or safer than peer-reviewed publications. Moreover, "neutral results" in ClinicalTrials.gov can easily mislead a lay public. See the discussion on p. 19 below.

Recommendations: Either wait until the NPRM has been implemented and perform a thorough cost-benefit analysis, or adopt a more finely tuned policy. If the NIH proposed policy simply required that all NIH funded trials register in ClinicalTrials.gov, we would endorse it wholeheartedly. There would be minimal additional cost because the registration and its concomitant ClinicalTrials.gov Quality Assessment takes a small fraction of the time that results reporting takes, and the vast majority of researchers already register any such studies because of their desire to publish in journals which follow International Committee of Medical Journal Editors policy. We believe that the NIH and the nation's public health would be better served by allowing the ClinicalTrials.gov regulations to be finalized; continuing the current NIH policy of "encouraging" registration and results reporting; and allowing the more critical drug and device trial reporting changes of the NPRM to become fully implemented before imposing a policy of results reporting on other NIH funded trials. An alternative targeted and efficient approach would be to require that all NIH funded research must, within three years of study completion, either (1) have a larger, follow up study underway, (2) have published results, or (3) post results in ClinicalTrials.gov.

The Draft Policy does not recognize the time and effort required to register and report results for clinical trials in ClinicalTrials.gov. Furthermore, there is a lack of recognition of the ongoing time commitments involved in maintaining compliance with FDAAA Section 801 and the NPRM as currently written. The proposed policy for requiring registration and results information for all NIH-funded clinical trials and the additional delineation that all clinical trials would be subject to the forthcoming proposed rule-making under FDAAA, do not account for the significant impact of financial and time obligations required by investigators and institutions to comply with this unfunded mandate.

Recommendation: We request that both the NIH and the FDA further recognize the time and effort required for both updating current study records and the ongoing updates that will be required under the proposed policy changes. We suggest that additional consideration be made

regarding the financial obligations that will be incurred by academic medical centers to ensure compliance of investigator-initiated research as necessitated by these proposals. We request that the NIH allow the time and effort required for ClinicalTrials.gov compliance to be included as a direct-cost on NIH grants.

III. Additional Comments and Limitations of ClinicalTrials.gov Website and Protocol Registration System Communication.

Despite hard work and ongoing improvements, the structure of the ClinicalTrials.gov database and the tiered mechanism for entry of data elements (in categories and sub-categories) is currently difficult to navigate for Responsible Parties conducting independent research at academic medical centers. Additionally, automated email communication from the Protocol Registration System requesting updates to study records could be significantly improved by being more specific in its content and being sent simultaneously to the PRS Administrator account for the institution, where there is one, as well as to the Responsible Party and the User account utilized to last update the study record. The inconsistency of the Protocol Registration System for relaying communication and reminders is of particular concern and potentially hinders compliance if a Responsible Party or other account holder is not available or an email address is no longer valid.

While the University of Michigan and our peer institutions are working diligently to improve our internal processes for faculty and staff off-boarding, we can do a better job to assure compliance if the Protocol Registration System communications to institutional user accounts had more built-in redundancy to prevent reminders and study record notices from falling between the cracks.

At present, the Protocol Registration System Administrator at a sponsoring institution is limited in the information that s/he can obtain from the database. This impedes the ability of a sponsoring institution to track study records and facilitate requests to Responsible Parties to ensure the information is accurate and verified.

Comment and Recommendation: We appreciate the increasingly efficient methods to sort, filter, and generate usable reports utilizing an extended set of data element fields from ClinicalTrials.gov for institutional management of study records and requests for updates. We ask the ClinicalTrials.gov system to continue to consult with academic medical centers and other users for ways to improve this further.

Data Quality, Integrity and the Limitations and Caveats Data Field: "Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data" – ClinicalTrials.gov results module.

If the National Library of Medicine, and our government more generally, want the data entered into its system to be as accurate and transparent as possible, the limitations and caveats data field ought to be expanded and promoted as a primary way for researchers to share a contextual basis for understanding and not misinterpreting study results. **Currently this field has a 250 character limit.** This is often not nearly enough to provide clarifications and cautions necessary for appropriate results interpretation

More data is not always better data. A particularly egregious case comes to light from the work of Professor Charles Seife of New York University in his recent article in JAMA "Research Misconduct Identified by the US Food and Drug Administration Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature" *JAMA Intern Med*. doi:10.1001/jamainternmed.2014.7774 published online February 9, 2015. In this piece, the author notes that

> Eight of 16 FDA inspections of sites involved in a clinical trial of rivaroxaban, a novel anticoagulant, had been rated OAI [Official Action Indicated]. These inspections had uncovered evidence of various transgressions, such as "systemic discarding of medical records," unauthorized unblinding, falsification, and "concerns regarding improprieties in randomization." Consequently, the entire study, RECORD 4 (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep-Venous Thrombosis and Pulmonary Embolism 4), was deemed unreliable by the FDA. (p. E4)

Professor Seife noted that publications about this trial did not mention the FDA findings. In fact, RECORD 4 is NCT00362232 on ClinicalTrials.gov, and, in the Limitations and Caveats section where the public would hope to find "Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data", no information is provided at all, let alone information relating to the FDA finding that the study results were unreliable. Without such caveats, the public at large would assume that a trial with more than 3000 participants would be reliable. Thus, it is far from clear that ClinicalTrials.gov presents a cleaner or more complete story that will help the public discern which data is reliable and which is not.

Recommendation: To make the data in ClinicalTrials.gov more understandable, studies with small sample sizes or studies which did not meet their enrollment goals should explain the impact of their small size on data interpretation. Additionally, all studies should have a regulatory obligation not only to correct inaccuracies as required in Sec. 11.66, but also to identify any concerning federal findings associated with the data collection. The caveats and limitations section should be expanded to at least a 200-word field to allow for careful and nuanced explanation of these issues. Arguably, certain sorts of caveats, such as an FDA determination that the data was deemed unreliable, might even warrant sequestering the record so that in a place where its data cannot be automatically downloaded for meta-analyses.

IV. Concluding Remarks

The University of Michigan agrees with the goals of the proposed regulatory and policy changes to promote data sharing and enhance transparency in clinical trials, to mitigate publication bias in scientific research and of course, to promote public health. However, as the seven-year period that it has taken NIH to create the results reporting system and draft these regulations suggests, major change requires gradual and thoughtful implementation. ClinicalTrials.gov is a constantly improving system, and we appreciate the ongoing efforts made by the National Library of Medicine staff to make it more efficient, transparent, and user friendly. However, it is still far from mature. Imposing short timelines for uploading substantial new types of information into ClinicalTrials.gov, combined with the lack of a rigorous peer review process along with other ever-increasing regulatory and policy burdens create converging risks of inadequately vetted data being broadly disseminated to the public on a federally sponsored website, and researchers being distracted from important clinical and teaching obligations by choosing to reapportion energy toward technical regulatory compliance tasks.

We appreciate the intense dedication on the part of the clinicaltrials.gov staff as they work with our researchers and our administrators to continue to make the system manageable. We appreciate their participation in monthly phone calls to help our academic regulatory staff stay informed and aware of best practices. We are eager to continue working with NIH and the National Library of Medicine in thinking through and developing best practices to make this system as helpful to our public as we can without becoming a source of misinformation or confusion.

Sincerely,

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