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Director
National Institutes of Health
9000 Rockville Pike
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March 20, 2015

RE: RIN 0925-AA52
Docket Number NIH-2011-0003
Proposed Rule - Clinical Trial Registration and Results Submission (November 21, 2014)

Dear Dr. Collins,

The Multi-Regional Clinical Trials Center (MRCT Center), based at Harvard University, has three primary goals: (1) to improve national and international standards for best practices in the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; (2) To simplify research through the use of best practices; (3) To foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research. The MRCT Center at Harvard does not fund, plan, conduct, or monitor clinical trials, but rather studies their regulatory, practical and ethical aspects, in order to improve design and conduct of clinical trials. The MRCT Center at Harvard has convened a number of working groups, including a group to study ways to facilitate greater access to participant-level clinical trials data while maintaining the security of private health information and a separate working group to plan and hold a conference in late March 2015 designed to promote shared governance and a shared data platform for a wide variety of industry and academic sponsors of clinical trials.

In this capacity, the MRCT Center at Harvard applauds the proposed rule's expansion of result reporting requirements to include trials involving drugs and devices not yet approved, licensed or cleared by the FDA. This new policy will help eliminate reporting biases, aid patients in deciding whether to participate in a comparable clinical trial, and ensure that trial participants have access to the results of the study in which they participated. Further, it will inform future research; redundant or potentially ineffective trials will be reduced and participants would not be exposed to unnecessary risk.

While we support the proposed rule, we wish to submit the following focused comments for your consideration.

Comments on Publication of Non-Technical Summaries - FR 69581

In response to the NIH's invitation for comments on the merits of such mandate, we provide the comments below. We also include a web-link to the *MRCT Center at Harvard's Return of Results Guidance Document* and the companion document *MRCT Center at Harvard's Return of Results Toolkit* (<http://mrct.globalhealth.harvard.edu/file/342726> and <http://mrct.globalhealth.harvard.edu/file/341171>). This guidance document reflects contributions from a variety of stakeholders including industry, academia, patient advocacy and non-profit centers. It addresses challenges that sponsors may face in returning non-technical summary trial results to research participants. The toolkit includes sample summaries and guidance regarding the use of non-promotional language.

1) Non-technical narrative summaries will provide numerous benefits to participants and their families.

The MRCT Center at Harvard appreciates the NIH's measured analysis of the benefits and risks of requiring responsible parties to submit non-technical narrative summaries of clinical trial results. The MRCT Center at Harvard believes that non-technical narrative summaries would be invaluable to clinical trial participants and their families. Participants expect that their contributions and sacrifices will result in tangible progress in the knowledge and treatment of their condition. Providing accessible and understandable summaries of the results of a participant's study is one way that the research community can meet this expectation. Summary results may also provide closure to participants, some of whom have been enrolled in a trial for many years. Participants will better understand how their study has contributed to scientific progress; such transparency will further promote public trust.

2) Non-technical narrative summaries should comply with established health literacy and health numeracy principles.

Non-technical narrative summaries will have maximum impact if they are written in compliance with health literacy and health numeracy principles. Health literacy principles include the use of short active-voice sentences, familiar vocabulary, descriptive headings and subheadings, and bullet points.¹ Health numeracy principles include the proper use of graphs and tables, use of numerical examples, and the inclusion of absolute risk as context for relative risk.² These are critically important considerations and, in order to facilitate the use of health literacy and numeracy principles, we suggest that the NIH adopt language supporting this approach in its current communication. The MRCT Center at Harvard further urges the NIH to release guidance on how to format and write summaries that are easy to understand and follow these principles.

3) Non-technical narrative summaries can avoid being misleading if they are provided in the context of existing literature and non-selective results.

The MRCT Center at Harvard acknowledges the NIH's concern that a responsible party may selectively include certain outcomes and not others within a non-technical narrative summary, potentially misleading the reader. However, we believe that proper context for narrative summaries can avoid this

¹ See Appendix Three of the *MRCT Return of Results Guidance Document*

² See Appendix Four of the *MRCT Return of Results Guidance Document*

risk and that appropriate focus on the primary endpoint—and the endpoints of importance to the participant—is critical. Those results should be non-selective and stated in a neutral voice without reference to safety and efficacy. However, the MRCT Center at Harvard believes that inclusion of all data, all secondary endpoints, and all “other” endpoints will be confusing rather than clarifying to the participant. Many secondary endpoints should not be included in the non-technical summary; only secondary endpoints that have a safety implication or may be impactful to participants should be included. The party responsible for posting non-technical narratives should be instructed to include summaries that are truthful, accurate, and non-selective or misleading. The language should be simple, factual, neutral and in its description. We further suggest the NIH (or the summary writer) provide a disclaimer at the beginning of each narrative summary stating that all outcomes may not be included within the summary and, if relevant, that full results can be found in tabular format elsewhere on clinicaltrials.gov. Further, the NIH should consider random audits of narrative summaries that exclude endpoints to verify that the responsible party is only including or omitting outcomes for proper reasons. Simply including all secondary endpoints (and it is not unusual to have >10-20 secondary endpoints) is not the answer; requiring such inclusion would be to the detriment of participant understanding.

- 4) The Food and Drug Administration should provide guidance on how to avoid the use of promotional language when writing non-technical narrative summaries.

The MRCT Center at Harvard strongly believes that non-technical narrative summaries can be written using neutral language that is not promotional in nature. Our team has written a short Neutral Language Guidance included in the *MRCT Return of Results Toolkit* on what language to consider and what to avoid when writing a non-technical summary.³ To facilitate the use of neutral language, we recommend that the Food and Drug Administration’s Office of Prescription Drug Promotion release guidance on how to write summaries that are non-promotional. We recommend further that the FDA further provide resources including user-friendly tools and templates to facilitate the implementation of and compliance with the final Regulation.

- 5) The NIH should work with the International Committee of Medical Journal Editors (ICMJE) and major journals to ensure that non-technical narrative summaries are not considered a “prior publication.”

Under its current recommendations, “the ICMJE will not consider as prior publication the posting of trial results in any registry . . . if results are limited to a brief (500 word) structured abstract or tables.” This 500-word exception is not sufficient to cover most non-technical narrative summaries. Therefore, the NIH should work with the ICMJE and other journals to expand the prior publication exception to include such non-technical summaries regardless of length. The 500-word cap and the limitation of the exclusion to “abstract(s) or tables” are arbitrary limitations and, unless changed, will pose a significant problem for investigators (and sponsors). Publication in the peer-reviewed literature is essential for communication of complete and detailed results of the trial to a scientific audience. The timely and appropriate return of results should not then undermine peer-reviewed publication. Thus, we recommend that the NIH choose a deadline for submission of narrative summaries that allows sufficient time for sponsors to publish their results in a journal prior to the deadline.

³ See MRCT Return of Results Toolkit

Comments on Results Submission Deadlines - §11.44

1) Extension of Deadline For Submission of Results After Initial Approval, Licensure or Clearance

Under §11.44 (a)(2), the responsible party must submit clinical trial results within 30 days of the date of approval licensure or clearance of a product. This deadline creates the possibility that responsible parties have much less than one year to prepare clinical trial results for submission. In such situation, the MRCT Center at Harvard requests that the NIH provide extensions for those responsible parties that have insufficient time to prepare results for submission.

2) Implementation of Single Deadline For Primary and Secondary Outcomes:

Under §11.44(d) of the proposed rule, the responsible party for a clinical trial of an unapproved product must submit clinical trial results within one year of the “completion date,” which is defined in §1.10 as “the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome.” The proposed rule allows for the submission of partial results if data collection for a secondary outcome extends beyond the above defined “completion date.” The deadline for the submission of the results for this secondary outcome is one year after the date on which the final subject is examined for the purposes of the secondary outcome.

MRCT Center at Harvard believes that such bifurcation of deadlines for primary outcomes and secondary outcomes places unnecessary burden upon sponsors (academic, industry, and non-profits) by requiring that they conduct the compilation process multiple times. Further, partial submission may be misleading or confusing for those accessing trial results online before the results for all outcomes have been submitted. We urge the NIH to redefine “completion date” as the date of the end of study last patient last visit, regardless of whether this visit is pertinent to the study’s primary outcome. This will align the NIH deadline with the European Union Clinical Trials Registry deadline for unapproved products.

Comments on Standard Data Formats and Submission Procedures - §11.48(a)(3) and FR 69583-69584

The MRCT Center at Harvard agrees with the NIH that the structured tabular data entry system currently found on clinicaltrials.gov provides maximum flexibility for results submission, permits an effective search engine, and facilitates cross-trial comparisons. However, this data entry process places significant burden upon responsible parties by requiring them to manually place individual result data points into the website or XML file. This burden is further compounded when the responsible party must comply with a separate data format when submitting to the Food and Drug Administration (and, additionally, other global regulatory agencies). Therefore, we urge the NIH to amend the proposed rule to adopt a standard data format consistent with CDISC SDTM and ADaM Data Submission Standards, to which the Food and Drug Administration has already committed. This would allow sponsors to create one results file that is in compliance with both NIH and FDA standards. Further, this requirement would encourage investigators who do not submit to the FDA but who nevertheless conduct clinical trials to also adopt the CDISC Data Submission Standards, creating greater harmonization across the clinical trials enterprise, further allowing cross-trial comparisons and analytics on pooled data.

Comments on Attribution Regarding Adverse Events

We noted that initially considered requirements for SAEs and causal relationship to the intervention does not appear in the final proposal. We agree with this omission as there is tremendous variability and lack of consensus with respect to the optimal methodology for causality determination. The determination at the individual level may be extremely subjective based on investigator experience and will not add significantly to the interpretation of summary data available after the trial is complete.

Comments on Mandatory Expanded Access Reporting §11.28(c)

Under the proposed rule, if expanded access is available for a drug under study, an expanded access record must be submitted. This change from a previously optional field to a mandatory field is a welcome change that will increase transparency in the now complex expanded access process. This proposed change will directly benefit patients with serious conditions and life-threatening conditions by inclusion of an easily searchable field in the database linking multiple applicable clinical trials to the same expanded access record.

Comment on Corrections of Clinical Trial Information – §11.66(a)

Under §11.66 of the proposed rule, a responsible party must correct errors “not later than 15 calendar days after the date on which the responsible party becomes aware of the errors or on which NIH informs the responsible party of the errors, whichever is earlier.” The MRCT Center at Harvard advises that this 15 calendar days is too short a window for a responsible party to repeat statistical analyses and undergo internal review processes. We request that NIH consider a change the timeframe to 30 calendar days.

The MRCT Center at Harvard thanks the NIH for the proposed rule and we appreciate the opportunity to provide comments for your further consideration. We hope the agency finds these comments helpful as you finalize the rule.

Respectfully submitted,

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On behalf of the Multi-Regional Clinical Trials Center at Harvard University