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Submitted electronically at www.regulations.gov

Margaret A. Hamburg, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

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RE: Document 2014-16492, Draft Informed Consent Information Sheet: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Released July 15, 2014, Docket 2006-D-0031

Dear Dr. Hamburg,

The Harvard Multi-Regional Clinical Trials Center (Harvard MRCT), based at Harvard University, has an overarching goal of improving 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; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research clinical trials. In this capacity, we welcome the FDA guidance for IRBs, clinical Investigators and sponsors on informed consent. We applaud the clarifications offered in the guidance and appreciate the focus on the informed consent process and understanding, and of the considerations for inclusion of individuals of low literacy and numeracy, non-English speakers, and vulnerable populations. We appreciate the flexibility offered by the FDA to engage in consideration of alternative methods of consent, as we believe that new technologies may enhance understanding, help to standardize content and delivery, and be useful in a global context. While we support the intent of most of the document, we wish to submit a number of focused comments for your consideration.

1) The document refers, at various times, to the informed consent form (ICF), the consent interview, the consent process and the consent discussion. In a number of sections, it is not clear to the reader whether the FDA is referring to the consent discussion or the ICF; clarification as to when a recommendation applies to the discussion or to the form would be helpful. Further, Harvard MRCT respectfully suggests that the term “consent interview” be replaced by “consent discussion” to reflect the appropriate and respectful engagement of the participant.

2) In recent years, the informed consent form has evolved from a “patient-centered form” toward one that is “sponsored-centered” or “institution-centered” whereby the form is so lengthy and detailed that the salient points required by participants to make an informed decision are lost. We agree that this is an opportunity to encourage emphasizing key elements such as risks and benefits and removing

unnecessary items such as lengthy lists of procedures. The ICF has evolved to serve the dual purpose of explaining the key elements essential to the decision and to limit and circumscribe institutional and sponsor liabilities and responsibilities. We therefore welcome the attention that the FDA has placed on content, simplicity, and health literacy.

a) We believe that all participants will benefit from informed consent discussions and documents that are readily understandable and follow principles of health literacy. Low literacy is not equivalent to poor health literacy. The examples of text that the FDA has used in its guidance should similarly reflect these principles and should be modified to be consistent with an 8th grade reading level (see for instance, Section III.6 p. 11-12). It would be helpful to provide greater guidance or refer the reader (by footnote) to sources of health literacy principles. Further, we suggest that consent writers subject each document intended for participants (e.g. recruitment materials, ICF, additional information, return of summary results) be subjected to readability tests such as Flesch-Kincaid, Gunning-Fog, and SMOG. This directive from the FDA would be consistent with the regulatory language that states that the information "shall be in a language understandable to the subject or representative" (21 CFR 50.20). The role of the IRB is to review such content for readability.

b) In the same context, we believe that the guidance should direct the reader to specific resources (by footnote) for assistance in simplifying estimates, risk, and numerical principles and presentations. Such numeracy resources exist, and the FDA should include examples that in the guidance document of simplified numerical presentations.

While we agree with the principle as stated:

If describing every procedure would make the consent form too lengthy or detailed, FDA recommends providing the general procedures in the consent form with an addendum describing all study procedures. It may be helpful to provide a chart outlining what happens at each visit to simplify the consent form and assist the subject in understanding what participation in the clinical investigation will involve. FDA believes that removing procedural details from the consent form will reduce its length, enhance its readability, and allow its focus to be on more important content, such as the risks and anticipated benefits, if any.

We believe that a 'chart' may be difficult to interpret for many participants, particularly given the complexity of many research studies. If such a chart conforms to health literacy principles, an example would be helpful. We suggest that the FDA model the inclusion of graphics rather then complex and dense tables.

3) Given the appropriate attention placed on participant understanding of the informed consent discussion and document, Harvard MRCT recommends that the FDA suggest the use of additional methodologies to ensure comprehension. In addition to the resource-intensive IRB monitoring of the informed consent discussion, methods such as "teach-back" and use of graphic, video, and other modalities should be encouraged.

4) Harvard MRCR is particularly concerned with the expectation that the investigator explain the alternatives to the proposed research in any significant detail. We recommend that FDA reconsider and clarify the guidance in Section II.B. Specifically:

   a) We believe that only general information about alternatives should be in the consent form; any specific information about alternatives should be a part of the consent discussion, not the consent form, in order to protect the simplicity and readability of the ICF.
   b) Harvard MRCT strongly disagrees with the threshold determination of "medically recognized standard of care" being "one evidenced by publication in a peer-reviewed journal" (footnote 17, p 9). Many experimental and innovative therapies are published in a peer-reviewed journal; indeed, many are not reproducible. A single publication does not reflect endorsement by the medical community. A more rigorous and reliable standard should be sought. We endorse the standard of "recognition by a professional medical society" and would agree with published "clinical guidelines" or "clinical pathways."
   c) The FDA should clarify whether alternatives to the research are based on the local or community standard of care or all available care options, many of which may not be realistically available to the participant and how that determination should be made.
   d) Section III.B.4 states that "Standard of care may include uses or treatment regimens that are not included in a product's approved labeling…." Harvard MRCT is concerned about sponsor-initiated and sponsor-monitored ICFs that recommend use of an approved product for an unapproved indication or method. This concern is heightened by the lack of a more rigorous definition and threshold for "standard of care."
   e) It would be helpful for the FDA to provide examples of "potential consequences of these differences in care" (Section III.B.!) and a definition of "reasonably foreseeable" (Section III.B.2) risks. Further, we recommend that the FDA discuss the application of their definition to both anticipated adverse events ("side effects," in common parlance) and unanticipated adverse events. How are rare, serious but known (and thus anticipated) adverse events differentiated from unanticipated adverse events, and how is the "reasonably foreseeable" threshold applied?
   f) Detailed discussion of risks and benefits of alternatives to the research is best explained by the health care provider, not by the research investigator.
   g) We note, with concern, the potential lack of harmonization with OHRP (footnote 16, p.9) and request that the government agencies harmonize their guidance. The regulated community, most often functioning under both OHRP and FDA regulations, deserves nothing less.

5) Harvard MRCT recommends that the FDA provide a definition of "reasonably foreseeable" (Section III.B.2) risks. Further, we recommend that the FDA discuss the application of their definition to both anticipated adverse events (side effects in common parlance) and unanticipated adverse events. How are rare, serious but known (and thus anticipated) adverse events differentiated from unanticipated adverse events, and how is the "reasonably foreseeable" threshold applied? We believe that it is important to provide potential participants with information that would most likely impact their decision to enroll in the research.

6) Harvard MRCT is deeply appreciative of the explicit inclusion of directives for appropriate enrollment of non-English speaking participants. We strongly disagree, however, with the specific recommendations made by the FDA with regard to unexpected enrollment of these potential participants, as we believe that the unintended consequence of the guidance as written will lead to under-enrollment of participants whose primary language is not English. Specifically:

    a) We do not appreciate the advantage or benefit of the required involvement of the IRB chair or their designee. Investigators are well positioned and responsible for protecting the rights and welfare of the participants and are able to determine whether the prospective participant is able to understand the nature of the research and provide informed consent. Further, IRB chairs may have much less experience than investigators in dealing directly with subjects and assessing understanding. Only in cases where the investigator requests advice from the IRB chair or designee should that involvement be sought. Prospective engagement of the IRB chair or designee is burdensome, will result in delay (if such a person cannot be found immediately) and potentially inhibit enrollment.
    b) Further, the requirement in step 3 that the IRB-approved English version of the long form "must" be translated will require time and resources that are not readily available, particularly in not-for-profit and academic settings. This requirement reaches beyond the regulations and will be a significant disincentive to enroll individuals who are non-English speakers.
    c) We encourage FDA to recommend medical interpreters only in situations where the risk of the study is consistent with this resource demand and if the presence of the medical interpreter will significantly enhance subject protections. In a low-risk setting, as in registry studies, family members, staff members, and patient advocates may appropriately serve this function.

7) We appreciate the recommendation that no participant be enrolled in more than one clinical investigation, however Harvard MRCT believes that further clarification of this recommendation is required. We believe that the intent of the recommendation is to limit the number of interventional, biomedical trials—and perhaps further limited to FDA-regulated interventional trials---and not applied to clinical investigations for which an informed consent is required more generally. Participants often consent to biorepository contributions, follow-on observational studies, concurrent behavioral studies, etc. Further, participants can be appropriately engaged in more than one clinical investigation in certain medical conditions, such as cancer therapies.

8) Harvard MRCT has been involved recently in discussions on return of general research results to participants. We have been working to align and harmonize approaches of multiple stakeholders to develop approaches for participant research summaries, including the content, process, logistics, and other considerations. We plan to engage the FDA more specifically in this work in the future. We were heartened to see that the FDA endorsed this expectation, saying "Aggregate research results should be returned to subjects in a clear and comprehensible manner." (Section V.K p.41). Additionally, multi-regional clinical trials will need to conform to EU regulations requiring return of results. We believe that certain clarifications and guidance be offered by the FDA. Specifically:

    a) A definition of "aggregate" should be provided. Is the intention to provide results beyond that required by FDAAA to be posted at ClinicalTrials.gov? Does the FDA anticipate that results be communicated for clinical trials not included in the CT.gov requirements (e.g. Phase I trials)?

b) Who should be preparing the aggregate results and in what format?
c) FDA should provide examples of language that would be considered non-promotional.
d) Does the FDA intend to review the research summaries to ensure that the language is considered appropriately balanced and not promotional? Will that review be timely?
e) If not, will the sponsor or institution face sanctions by the FDA?
f) If the investigator or research site is anticipated to prepare the research result summary, how will consistency of information be ensured? For example does the FDA expect specific source documents to be used in the creation of the summary?
g) Will the expectations of the FDA differ for FDA-regulated investigator-initiated trials?
h) Who should communicate the results to the participants at the end of trial? If the sponsor, does the FDA anticipate that the sponsor will retain personally identifiable information about the participants to execute on its responsibility to return results? If the research site and/or investigator, will the sponsor be responsible for ensuring that the communication has been achieved?
i) The results will be returned after the study is closed. The IRB therefore no longer has oversight responsibilities for the trial or the return of aggregate results. FDA should clarify this point.
j) Harvard MRCT believes that participants should be offered a choice as to whether to receive aggregate results. We believe that that choice should be made not as a part of the initial consent discussion but later, perhaps at last study visit.
k) Return of aggregate research results will prompt participants to ask for their individual results. FDA should offer guidance as to what can, should, or must be returned to participants regarding their individual results, study arm, and other findings.

Harvard MRCT thanks the FDA for the Draft Guidance and we appreciate the opportunity to provide comments for your further consideration. We hope the agency finds these comments helpful as you finalize the guidance.

Respectfully submitted,

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