Brigham and Women's Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Submitted via Regulations.gov Docket No. FDA-2022-D-2997

Re: Draft Guidance, Key Information and Facilitating Understanding in Informed Consent

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) commends FDA on its draft guidance entitled "Key Information and Facilitating Understanding in Informed Consent" ("the Draft Guidance").

The MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it is an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. While the MRCT Center often collaborates and interacts with regulators around the globe, we have not discussed the comments provided herein with any regulatory agency. The responsibility for this document's content rests with the MRCT Center's leadership, not with its collaborators nor with the institutions with which its authors are affiliated.[1]

We share your vision for promoting health literacy and view the Agency's guidance on this issue as welcome and timely. To that end, we would first like to thank the Agency for endeavoring to extend this guidance and, second, to take the opportunity to provide some limited feedback on the proposal presented in the Federal Register at 89 Fed. Reg. 15094-96 (March 1, 2024). Our comments are offered only to strengthen the Draft Guidance, as its issuance is of paramount importance.

Overall Comments
The MRCT Center appreciates that FDA reemphasized several important considerations with which we agree:

1. The importance of harmonizing the expectations—whether regulations or guidance—between FDA and OHRP. As most US institutions are engaged in research funded or conducted by federal funds as well as in FDA-regulated research, consistent expectations make it easier to establish systems, policies, processes, and oversight across the organization. Of course, consistency in the US may not result in convergence with international regulatory expectations of informed consent documents.
2. The reminder of allowable flexibility in the implementation of the Draft Guidance, and the specific acknowledgment that all required elements of informed consent must be included in the

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key information section. It may be helpful for FDA to emphasize that investigators and organizations should document contemporaneously why a different approach was taken, both for learning and for responding to subsequent questions, should they arise.

3. The clarity with which FDA states that information in the key information *need* not be repeated in the informed consent form.
4. The emphasis on plain language approaches to communication, not only in the key information section but the entire informed consent document.
5. We encourage the FDA to mention explicitly that access to the individual's participant data may be viewed as a benefit (and conversely, data that are not provided may discourage participation and, therefore, be mentioned as key information). The participant should also be told (in either the key information or the informed consent document itself) whether they will have access to aggregate results from the trial.
6. The very practical nature of the Draft Guidance, including the hypothetical key information section example.

The MRCT Center does have some suggestions for strengthening the document that apply generally:

1. The Draft Guidance repeatedly refers to plain language and further explication of and references to plain language principles and application would be helpful. Plain language concepts such as using everyday words (e.g., "use" not "utilize"), short sentences, active voice, simplified terms and definitions, readability testing both by standard measures and user testing, clear design, numeracy, visualization, and cultural considerations, among others. Further guidance on how to assess whether plain language principles, in the service of understandability, would be helpful.
2. The Draft Guidance should emphasize, in our opinion, the importance of testing key information and informed consent more generally for accessibility (e.g., font choice, font size, color contrast, text spacing, line height, saturation, and screen readability).
3. Often overlooked, the necessity of maintaining plain language and accessibility in translated documents should be mentioned.
4. The Draft Guidance should emphasize the dynamic nature of the informed consent process that should accompany the informed consent document with its key information section. The reader should not assume that the presence of key information replaces or minimizes the importance of the informed consent discussion.
5. Whom to contact in the event of adverse events, questions, and follow-up might be considered key information in some settings.
6. While we understand that the US regulations refer to participants as "subjects," we encourage FDA to use the term "participants" unless specifically quoting either the regulations or law.
7. FDA should discuss and reference "Tier 1, 2, and 3" information and how the reader would determine which information belongs in which tier.

Specific comments:

Key Information Section

Section III.A recommends the development of "innovative ways…to provide key information" to prospective trial participants (p 4, ln 103-04) and suggests key information may be presented by interested parties via "alternative media, such as illustrations, video, and electronic tablets." (p 4, ln 109-10). We are encouraged by the specific endorsement of alternative consent methods. It would be helpful for the Draft Guidance to clarify whether a witness must verify that the alternative media presentation has been appropriately accessed and/or understood. Do videos providing key information qualify as "oral presentations," and, if so, will witnesses be required to sign informed consent forms following video presentations? As experience grows with alternative media formats, the current Draft Guidance may require further expansion and clarification.

The MRCT Center understands FDA's encouragement that the key information section be "relatively short," and we agree that specifying length or limitation on the length would not permit the flexibility needed for the range of complex research clinical trials. It should be noted that health literacy experts agree that length is only one dimension of plain language and understandability. It is more important to include information that is explained simply, and translating complex concepts to clear information may take more words (and therefore length). Further, appreciation of design elements, including spacing, font size, and splitting a complex sentence into two, may all add length to the section—but also clarity.

We recommend reconfiguration of the Draft Guidance such that Section IV.B.3, "Understandable Language," extends to the entirety of the informed consent form covered by the Draft Guidance.

We suggest that FDA encourages the use of imagery, tables, and other visual methods to present information. Use of participant calendars, a table of research procedures, and other presentations can be helpful in promoting understandability.

The MRCT Center requests FDA reconsider the recommendation for page numbers to link sections of key information to the more complete section of the informed consent document. Page numbers do not remain consistent from revision to revision or in translated documents, and are subject to change for other reasons (e.g., font size, accommodations, etc.) Instead, we suggest alternative methods of linkage (e.g., a specific section header that is unique to that section of the informed consent or a hyperlink) should be considered.

While the "bubbles" are visually aesthetic, there are other methods that FDA might consider (e.g., section headers and bold font). Bubbles can be restrictive and render the inside content difficult to change if change is necessary. Other designs may be easier to work with.

Appendix

We offer some comments on the key information for the hypothetical clinical trial.

Purpose of the research - Our experience with patients and advocates has demonstrated that the words safe and effective are not well understood, either because the terms are too absolute (e.g. interpreted as completely [100%] safe and effective) or because they don't speak to or validate the lens through which marginalized populations have experienced healthcare. Questions such as, "Is this safe for people **who look like me**?" and "Does this work for people **who look like me**?" prevail. Generally, we suggest clarifying that the safety and efficacy assessment are continuously being evaluated and analyzed through the product's life cycle, clarifying that the risks and benefits continue to be explored

In the section on *Reasonable foreseeable risks and discomforts*, perhaps the inclusion of a risk that is more of a discomfort/inconvenience but could impact someone's life disproportionately to the adverse event would be important.

Under the '*benefits'* section, we would not recommend not adding detail on how the groups are assigned nor information about randomization. What is important is the concept that the individual will be assigned to one treatment group, comparator, or another and not be permitted to choose.

Under the section on *costs*, the statement that "you may incur costs" may be insufficient for such a complex healthcare system and may be a good reason why participants choose not to participate. Can further guidance be included?

We appreciate the opportunity to comment and FDA's commitment to providing practical guidance to clinical researchers.

Please feel free to contact the MRCT Center (sawhite@bwh.harvard.edu or bbierer@bwh.harvard.edu) if we can be helpful or if you wish to discuss.

Respectfully submitted,

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