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

June 18, 2024

Notice #NOT-OD-24-112
Submitted via the NIH Comment Form

Re: FDA-NIH Terminology for Clinical Research

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the draft glossary entitled "FDA-NIH Terminology for Clinical Research" ("the Draft Glossary") released as a joint effort by the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), collectively "the Agencies." Improving the conduct of clinical research is fundamental to the work we do, and we believe the Agencies' efforts to standardize terms that have arisen alongside the rapid innovations in clinical research in recent years will improve the conduct and communication associated with clinical research in the U.S. and elsewhere.

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, 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. As an independent convener, the MRCT Center engages with diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies to address these issues. 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]

The MRCT Center has long been a champion of health literacy, and our plain language Clinical Research Glossary has been adopted as a global standard by the Clinical Data Interchange Standards Consortium (CDISC) and indexed within the National Cancer Institute Thesaurus. We share your vision for promoting a shared language among clinical research stakeholders and welcome the Agencies' guidance on this issue as critical and timely. To that end, we would first like to thank the Agencies for endeavoring to extend this guidance and, second, to take the opportunity to provide our feedback and concerns on the proposal with the intention of clarifying and extending the guidance.

[1] Brigham and Women's Hospital, Mass General Brigham, Harvard Medical School, Harvard University.

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General Comments on the Draft Glossary's Scope

Title, Scope, and Governance

The Introduction to the Draft Glossary describes the common thread among the 37 terms included in the document as "terms related to innovative clinical study designs, including studies using real-world data (RWD) to generate real-world evidence (RWE)." (p1) As the Introduction explains, the spirit of Draft Glossary is to facilitate communication across the clinical research enterprise by ensuring that stakeholders share a "common vocabulary" and are thus able to communicate with greater clarity and precision with one another.

The current title, "FDA-NIH Terminology for Clinical Research," suggests a considerably larger scope than either that described in the Draft Glossary's introduction or that covered by the 37 terms. For clarity, we recommend amending the Draft Glossary's title to reflect its scope more explicitly – e.g., "FDA-NIH Innovative Clinical Research Terminology for Researchers" or something similar.

Further, clarifying the scope of what exactly falls under the umbrella of "innovative clinical research" would ensure that expectations for the use of this Draft Glossary are met. Certainly, terminology related to clinical research involving precision medicine, telehealth, digital health technologies, and artificial intelligence, to name just a few, could be considered innovative and, we suggest, should be included (see below).

Given the limited number of terms that are defined, it would be helpful for the Agencies to describe how the terms were selected, the process used to define the terms (including public engagement), as well as address governance and maintenance, such as whether the Agencies plan to update the Glossary periodically. We recommend mentioning whether there will be opportunities to recommend new terms for consideration to the Agencies and, if so, the process envisioned.

We commend the effort put into assembling the content in this Draft Glossary, and given our experience in developing standardized terminology, recommend including an example sentence and more information demonstrating the application of the terms in real-world scenarios. Developing cross-references within the Draft Glossary to related terms would also support researchers in navigating and understanding interconnected concepts. For example, linking "decentralized clinical trial" with "virtual trial," "remote monitoring," and "telemedicine" would be important. Similarly, clarifying if there is a difference between certain terms that appear to be used interchangeably (e.g., healthcare provider and healthcare practitioner) or are apparently highly similar to one another (e.g., point-of-care trials, pragmatic trials, real world trials) would be helpful.

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Finally, as this appears to be a standards development process, we also note that such efforts start with a landscape and gap analysis to avert any inadvertent disharmony being created between this resource and existing CDISC terminology resources (including CDISC Glossary, CDISC Submission terminology (SDTM, ADaM, etc.) that are required for use by the US FDA, and our own MRCT Center Clinical Research Glossary. Is this Terminology intended to be aligned with international standards (e.g., CIOMS, ICH)? Clarification of these relationships and any differences would be helpful.

It is therefore recommended that the Draft Glossary include these topics either in the body of the work or as an appendix to support transparency of the process and to increase confidence in the Draft Glossary's content.

Audience

The Draft Glossary's Introduction (p1) describes the FDA-NIH Clinical Research Working Group (CRWG) that composed the glossary as including "statisticians, epidemiologists, pharmacologists, clinicians, biomedical engineers, and policy experts" who were convened to develop a resource "to bring clarity to terms that are inconsistently used within the scientific community." The definitions were developed *by* sophisticated clinical research professionals *for* clinical research professionals. Later in the Introduction, however, the Draft Glossary explicitly defines its scope as "intended to facilitate communication within the clinical research community." We recommend that this sentence be changed to "…facilitate communication within the **professional** clinical research community." The definitions are highly technical and not intended for trial participants, a critically important stakeholder in the clinical research community.

As the MRCT Center's Clinical Research Glossary already contains four of the 37 terms included in the Draft Glossary (and three of the eight reference terms), we recommend that the CRWG coordinate with CDISC to ensure both (i) consistency across the international portfolio, and (ii) that the terms in the Draft Glossary are each assigned similarly standardized, accessible, plain language definitions for those occasions when non-technical members of the broader clinical research community must confront, interact with, and understand them.

While we recognize this Draft Glossary is an FDA-NIH resource, harmonization with ex-US efforts should also be considered. Based on the list of source citations, this resource appears to be fairly US-centric. It would be prudent, however, for the CRWG to harmonize with CIOMS, ICH, and ISO terminology standards and initiatives. A further important extension of the effort to harmonize terms and processes is to ensure that the ICH-M11 Working Group has each innovative trial design reflected in the electronic clinical trial prototype currently under development.

Finally, consideration should be given to language accessibility for non-English speaking researchers.

Recommended Terms to Include in the Draft Glossary

Given this important initiative, there are several terms that we believe would benefit from a common definition (or reference in the Appendix if the definition has been previously provided). These include (in alphabetical order):

1. Artificial intelligence
2. Bayesian Trial Design
3. Data federation (and/or federated data)
4. Data lake
5. Data warehouse
6. Decentralized Clinical Trial
7. Decentralized Clinical Trial Elements
8. Differential privacy
9. Digital health technologies
10. Digital twin
11. Estimand Framework
12. Estimands
13. External control arm
14. Extrapolation
15. Healthcare Practitioner
16. Healthcare Provider
17. Point-of-care trials
18. Precision medicine
19. Simple Trials
20. Synthetic arm
21. Telehealth
22. Virtual trial

And then, of course, there are a number of additional terms related to AI, ML, and generative AI that could be included.

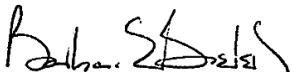
Conclusion

We appreciate the opportunity to comment on the Draft Glossary. It strikes us as a challenging and nuanced undertaking, and we value the Agencies' commitment to providing meaningful

guidance to clinical researchers. We look forward to seeing the updated final glossary. We would welcome the opportunity to work directly with the Agencies or to answer any questions.

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

Respectfully submitted,



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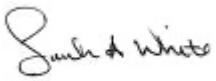

Sarah A White, MPH
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