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

December 13, 2024
https://www.regulations.gov/docket/FDA-2024-D-2052

Re: **FDA-2024-D-2052-0002**
Draft Guidance: Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice

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Center") appreciates the opportunity to comment on the Food and Drug Administration's ("FDA's" or "the Agency's") draft guidance document entitled "Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice," published at Fed. Reg. On Sep. 18, 2024, by the Department of Health and Human Services ("HHS" or "the Department"). This guidance is timely and reflects the changing environment of randomized controlled clinical trials (RCTs) for participants, clinicians, and sponsors.

The MRCT Center is a research and policy center that seeks to improve the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as 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. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.[1]

We commend the FDA's focus on enhancing accessibility and generalizability by embedding RCTs within routine care settings. This guidance represents an important step in leveraging real-world evidence (RWE) and real-world data (RWD) to make clinical trials more inclusive, accessible, efficient, and reflective of everyday healthcare settings. Below are recommendations to enhance the implementation of this guidance while maintaining scientific rigor, participant safety, and data reliability.

Recommendations

The ability to incorporate RWE and RWD into clinical trials is critical to achieving equitable healthcare innovations and ensuring that clinical research better reflects the diverse populations and contexts in which healthcare is delivered. The guidance's objectives to streamline clinical trial protocols by focusing on essential data collection (Lines 78–87, Page 3) are particularly timely, as they aim to reduce burdens on both participants and clinical sites while maintaining scientific rigor. Achieving these goals requires a careful balance between integrating trials into

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

Smith Center #771, 1350 Massachusetts Ave, Cambridge, MA 02138
Tel: 617-827-7413 | Email: bbierer@bwh.harvard.edu
75 Francis Street, Boston, MA 02115
www.MRCTCenter.org

routine clinical workflows and ensuring the accuracy, consistency, reliability, and validity of the data generated to meet trial objectives. While EHRs are valuable for preserving and accessing data, they are not inherently designed for clinical trials or for ensuring compliance with trial protocols. Therefore, methodological rigor is essential, including embedding trial-specific data requirements into EHR configurations, training providers to capture protocol-mandated data accurately and in a timely fashion, avoiding endpoints that rely on free-text entries, and implementing systems to monitor and address variability or inconsistencies in the data collected. This approach aligns with the draft guidance's emphasis on prioritizing objective measures to maintain scientific rigor. Further explanation and examples of practices to embrace and to avoid would be welcome.

One key challenge is ensuring data quality and consistency across diverse clinical settings, particularly when relying on routine clinical documentation (Lines 99–108, Page 3). Differences in healthcare practices and documentation methods could compromise data reliability and protocol adherence. Given the pressures on efficiencies in clinical care and the expense (and prioritization) of EHR modifications, it is unreasonable to anticipate that the EHR will be tailored to protocol needs. Therefore, prioritizing objective endpoints that are routinely collected in clinical practice will reduce variability and enhance data reliability. It would be helpful for FDA to provide examples of appropriate and problematic data elements to guide implementation.

While essential for minimizing bias, blinding and randomization present unique challenges in integrated trial settings. The guidance could emphasize hybrid approaches, such as using EHR-integrated randomization systems to streamline processes while incorporating independent reviews to maintain objectivity in outcome assessments and provide additional examples.

FDA does not address the ethical considerations of randomization, the challenge of explaining randomization in clinical care settings, or the reluctance of many HCPs to engage in that conversation. Acknowledging the HCP (and investigator) training and the patient education that will be necessary would be appropriate. The ICF should use plain language to outline data access, usage, and safeguards to help participants understand how their information will be collected, stored, and shared, including an explanation of any potential future uses of their data. The guidance could encourage sponsors to anticipate any secondary uses of data during the initial consent process, acknowledging that participants may not be available to approve or decline future uses.

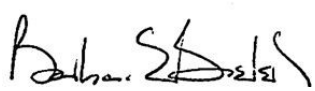
The use of EHRs and other sources of RWD introduces potential vulnerabilities in data privacy and security. These vulnerabilities can include unauthorized data access when shared across clinical and research platforms, misuse of data beyond protocol-specified purposes, inconsistent security practices due to EHR variability, and risks of re-identification as datasets are combined or shared more widely. In addition, certain information elicited in the research setting may not belong in the medical record; FDA should alert investigators and sponsors to consider these issues and strategies for mitigating these risks.

While the guidance references real-time EHR monitoring systems and automated alerts (Lines 412–417, Page 11) for participant safety monitoring, often AE reporting is a core critical-to-quality factor. FDA should encourage trials to incorporate practical systems (e.g., real-time EHR monitoring, mobile technologies, participant reporting tools) to identify and address AEs while navigating the practical challenges of implementing automated alerts directly within EHRs. Integrating these mechanisms into the foundational design of trials ensures that safety monitoring aligns with the protocol's objectives and maintains blinding where appropriate.

Importantly, we suggest that CDER Center for Clinical Trial Innovation (C3TI) explore the creation of a program to encourage sponsors, investigators, and participating sites to pilot different approaches and methodologies to integrated trials. Defining a pathway to allow experimentation, with metrics for assessing feasibility, data quality, participant safety, and integration into routine clinical workflows (Lines 274–278, Page 9), may encourage trial sponsors and investigators, HCPs and sites to explore – and learn from – this approach. Conducting pilots in diverse healthcare settings, particularly in low-resource areas that have historically lacked access to clinical research, could expand participation and equity in clinical trials.

Integrating RCTs into routine clinical practice holds promise for democratizing clinical research and accelerating evidence generation. Realizing this potential requires thoughtful strategies to ensure data integrity, participant safety, and compliance with regulatory and ethical standards. The recommendations outlined can help refine and operationalize this guidance, supporting the FDA's goal of integrating clinical trials more seamlessly into routine care.

Respectfully submitted,
On behalf of the MRCT Center:



Barbara E Bierer, MD
Faculty Director
On behalf of Sarah A White, MPH, Julia S Etkin, BA and the MRCT Center