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

Submitted June 20, 2024

Re: **Docket No. FDA–2023–D–5470**
Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products

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(MRCT Center) appreciates the opportunity to comment on the Food and Drug Administration's ("FDA's" or "the Agency's") Draft Guidance for industry entitled, "*Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products*," published at 89 Fed. Reg. 20207-09 (Mar. 21, 2024) (the "Draft Guidance"). Guidance on this topic is timely, welcome, and important to stakeholders across the entire enterprise as clinical research continues to evolve.

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]

The MRCT Center applauds the broader effort to promote high-quality and scientifically valid analysis using RWD to develop evidence using non-interventional studies for regulatory decision-making. The advice, including an understanding of data sources and data quality, identification of sources of bias, the need for design, and statistical pre-specification, among others, will serve the regulated community. Further, the Agency's direction to consider and explain the feasibility of alternative approaches prior to finalizing the non-interventional study design is important as is the encouragement to include a causal diagram.

We appreciate that the Draft Guidance is clear, concise, and straightforward. We offer a few comments below in an effort towards further clarification.

- It would be helpful to clarify whether and which elements in the Draft Guidance are unique to the use of Real-World Evidence ("RWE") in non-interventional studies versus interventional and other studies that use RWE. For instance, recognizing, mitigating, and/or eliminating confounders and sources of bias (p 3, ln 75-77) are important in any study and not unique to non-interventional studies. Similarly, many recommendations contained in Section III of the Draft Guidance are common across all studies (e.g., "finaliz[ing] the study protocol, including the research question of interest and rationale for the study design, before initiating study conduct" (p 4, ln 112-13), demonstrating "an in-depth understanding of the use of the drug(s) of interest and the outcome(s) of interest, as well as the capture of exposure, outcome(s), and relevant covariates in the proposed

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

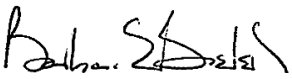
Smith Center #771, 1350 Massachusetts Ave, Cambridge, MA 02138 75 Francis Street, Boston, MA 02115
Tel: 617-827-7413 | Email: bbierer@bwh.harvard.edu www.MRCTCenter.org

study population." (p 4, ln 117-19)). It would be helpful, therefore, for the Agency to explain why these reminders are mentioned, whether and why they are particularly applicable to non-interventional studies, and/or whether there are specific and unique considerations in these trials.

- We encourage the Agency to include a more robust discussion of different types of bias, and their qualitative identification, quantitative assessment, and mitigation.
- Several recommendations in the Draft Guidance appear to echo parts of prior FDA guidance (e.g., *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products; Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products*; *Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products;* and others. We therefore suggest that the current Guidance (i) cross-reference the Draft Guidance to prior guidance documents where more detail might be found, (ii) highlight its unique contributions, or (iii) explain further its inclusion (e.g., for completeness).
- Guidance in Section III.E could be further developed. While the Draft Guidance lists several elements of a satisfactory SAP (p 7, ln 217-47), it would be helpful to provide further exposition of the bulleted list currently included.
- There are terms that would benefit from definition or reference (e.g., reverse causality), and clarification of terms that differ from other FDA Guidance documents (e.g., fit-for-purpose" versus "fitness for use.)
- We question whether there are different considerations for RWE-based non-interventional trials based on the purpose of the study: are there differences if the study is directed to address safety concerns, a new indication of an approved product, post-trial commitments, or other purposes? Are there differences in the context of rare or ultra-rare diseases? Are there differences if a study collects and uses primary data versus that which uses only previously collected data?

The MRCT Center appreciates the opportunity to comment on this Draft Guidance document, and we would welcome the opportunity to discuss it.

Respectfully submitted,



Barbara E Bierer, MD
Faculty Director, MRCT Center
bbierer@bwh.harvard.edu