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PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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April 28, 2023

Lauren K. Roth, JD
Associate Commissioner for Policy
Office of the Commissioner
Food and Drug Administration
19903 New Hampshire Avenue
Building 32, Room 4239
Silver Spring, MD 20993-0002

RE: Docket No. FDA–2022–D–2983 - Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products; Draft Guidance for Industry.

Dear Ms. Roth,

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s Draft Guidance for Industry, on "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products," published in the *Federal Register* on February 1, 2023.

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise appreciate the central importance of ethics to the advancement of science.

PRIM&R believes the FDA's draft guidance, which addresses considerations for the design, analysis, and validity of trials using external controls, is well crafted and will be extremely useful to the regulated community. PRIM&R notes, however, **that the draft guidance does not address ethical issues in studies involving external controls. Specifically, the guidance is silent on respecting individuals' consent for the use of their data that were collected for other purposes** (for example, data from other studies, or real-world data). The use of these data poses distinct challenges to institutional review boards (IRBs) charged with overseeing such studies. Below are additional recommendations focused primarily on consent issues that we

believe will not only enhance the utility of the guidance to both researchers and IRBs but also bolster public trust and confidence in research supporting FDA-regulated products.

The draft guidance clearly articulates considerations for the design and analysis of externally controlled trials when using patient-level data from other clinical trials or from real-world data (RWD) sources, such as registries, electronic health records (EHRs), and medical claims. It provides detailed information on factors and criteria that need to be considered when determining the suitability of an external control arm for a clinical trial, such as characteristics of the study population, attributes of treatment, assessment of outcomes, assessing comparability of data across arms, etc. The draft, however, does not provide guidance on study design issues that researchers need to explicitly address in their IRB protocols, nor does it provide guidance for IRBs that are tasked with reviewing studies involving external controls. For example, we recommend the guidance **include a section that both specifies factors that the IRB should take into consideration when evaluating the appropriateness of a proposed external control and advises investigator on the type of information they should include in their IRB protocols to describe the control selected and the rationale for selecting it.**

Below we recommend other information the guidance should highlight for researchers to include in their IRB protocol for trials with external control arms, to facilitate a thorough IRB review, including:

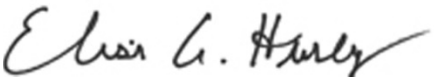
- Privacy Protections
    - Description of mechanisms that will be employed to ensure that data from registries, originally collected for non-FDA approval purposes (i.e., collected for healthcare), are used in ways that comply with applicable privacy requirements and minimize risks, when possible (for example, instituting measures to minimize risks of re-identification). This is particularly important when using RWD or registry data for clinical trials of rare diseases that afflict a very small population, which makes identifiability more feasible. Such information will assist the IRB in making determinations such as, if the proposed data use qualifies as human subjects research, whether it is exempt, and whether a waiver of consent is appropriate.
- Consent
    - Description of the provenance of the data and the conditions under which they were collected to ascertain the nature of the original consent so as to ensure that using the data as an external control does not violate subjects' consent, where applicable.
    - Detailed information in the protocol that will assist the IRB in determining whether consent can be waived and if it not, what type of consent is appropriate (e.g., broad consent, opt-in, opt-out), when external controls are sourced from RWD repositories such as EHR and claims data.
- Bias

- Recognizing and accounting for the fact that different approaches to obtaining consent such as opt-in versus opt-out can affect the representativeness of the sample and potentially introduce bias.
- Recognizing and accounting for bias that may be inherent to historical controls, such as previous studies that are known to have shortcomings related to clinical trial diversity.
- While creating synthetic data is a privacy enhancing or preserving mechanism that can be used to create external control data, researchers and IRBs must be cognizant of the fact that synthetic data can also perpetuate bias. Such inherent bias can impact not only the outcome of the study, but potentially have serious clinical implications for subjects in the experimental arm(s) of the trial. Thus, it is important for the study design to include details about steps taken to mitigate, if not eliminate such bias.

PRIM&R also recommends that the FDA guidance explicitly direct sponsors and investigators conducting clinical trials to include language that enables use of data collected in those trials as external controls in future studies, to ensure that appropriate consent is obtained. Finally, as FDA continues to work on harmonizing its regulations with the Common Rule, PRIM&R believes the guidance should clearly direct IRBs to review external controls in addition to the experimental arms of the study.

Thank you again for the opportunity to provide comments on FDA guidance. We hope that our comments are useful to OSTP in this effort. PRIM&R stands ready to provide any further assistance or input that might be of use. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Sincerely,



Elisa A. Hurley, PhD
Executive Director

cc: PRIM&R Public Policy Committee, PRIM&R Board of Directors