REAL-WORLD EVIDENCE ALLIANCE

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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Re: Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products; Draft Guidance for Industry; Availability (Docket No. FDA-2023-D-5470)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to comment on the draft guidance titled "Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products" ("Draft Guidance").[1] We are a coalition of real-world data ("RWD") and analytics organizations with a common interest in harnessing the power of real-world evidence ("RWE") to inform regulatory decision making to improve the lives of patients. Our members have deep knowledge and experience working with healthcare data across disease areas and patient populations, and we aim to bring these collective insights to bear in support of RWE policies.[2]

The RWE Alliance envisions a future in which data from electronic health records, administrative claims and billing records, product and disease registries, personal devices, wearables, and health applications will be used to generate evidence to support regulatory decision making related to medical product safety and effectiveness. To achieve these goals, the RWE Alliance advocates for policies that will (1) advance FDA's RWE Framework, (2) encourage the use of RWE to better understand treatment effects in underrepresented populations, (3) enhance opportunities for RWE organizations to consult with FDA, (4) increase communication on the generation and use of RWE, and (5) recognize the unique aspects of and opportunities for RWD/E.[3]

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[1] 89 Fed. Reg. 20207 (March 21, 2024).

[2] For information about our members, please see our website, https://rwealliance.org/who-we-are/.

[3] Additional information about what we believe is available on our website, https://rwealliance.org/what-we-believe/.

We commend FDA for releasing a Draft Guidance that provides comprehensive recommendations to sponsors preparing non-interventional study designs involving RWD. Section I of this letter provides general comments on the Draft Guidance, and Section II provides specific comments on topics addressed in the Draft Guidance.

I. General Comments on the Draft Guidance

We commend FDA for the approach taken in the Draft Guidance, which will help RWD and analytics organizations as well as sponsors navigate the opportunities and complexities that come with designing a non-interventional study using RWD. We appreciate FDA's acknowledgement that non-interventional studies using RWD can support the demonstration of substantial evidence of effectiveness and provide evidence of safety.

We also appreciate that the Draft Guidance describes important considerations for each stage of a non-interventional study—beginning with the early stages of forming a research question and study design and continuing with data collection and data analysis. The considerations described in the Draft Guidance help to establish the reliability and relevance of RWD used in a non-interventional study design and, as the Draft Guidance explains, are essential to establishing the data's fitness for use in generating RWE.[4] In the Draft Guidance, FDA uses the term "fitness for use" to refer to reliability and relevance assessments,[5] whereas, in other guidance documents, FDA uses the phrase "fit-for-purpose assessment."[6] We recommend that FDA clarify whether these terms are synonymous. We also recommend that FDA use a single defined term to refer to reliability and relevance assessments across all Agency RWE guidance to minimize confusion and ensure that stakeholders in the RWE ecosystem interpret FDA's guidance correctly and consistently.

We thank FDA for elaborating on key concepts from earlier RWE guidance, including sponsor engagement with FDA and pre-specification of a study protocol for non-interventional studies. It is particularly helpful that FDA clarified that sponsors do not need "detailed information on every attribute"[7] of the non-interventional study design and analysis at the time of early engagement with FDA. It is also helpful that FDA clarified that sponsors should discuss why alternative approaches were not feasible to answer a study question prior to deciding on a proposed study approach. We encourage FDA to approach future RWE guidance in a similar fashion, addressing both opportunities and complexities of using RWD/E in regulatory decision making and providing clear direction on FDA's expectations while maintaining appropriate flexibility.

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[4] Draft Guidance at 2.

[5] *Id.*

[6] *See* FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (2023).

[7] Draft Guidance at 4.

II. Comments on Specific Sections of the Draft Guidance

The following subsections provide our comments on specific sections of the Draft Guidance. For ease of reference, the headings for each subsection correspond to the headings used in the Draft Guidance.

A. Introduction

- In lines 24–34, the Draft Guidance distinguishes non-interventional studies from interventional studies, where the latter are defined as studies in which the protocol stipulates patient assignment to drug-related interventions. As part of this discussion, we suggest that FDA reaffirm[8] that non-interventional studies include studies in which there are no protocol-assigned treatments but there are protocol-directed assessments, which might be a part of routine care (e.g., laboratory tests, imaging procedures, patient-reported outcomes, blood draws). These types of studies can be important options for addressing questions about the natural history of a disease or condition and for augmenting available RWD to assess treatment effectiveness adequately.

- In footnote 8, the Draft Guidance expands on the assessment of reliability and relevance of RWD and explains that non-interventional studies often repurpose data obtained from clinical practice but that non-interventional designs "can also include the collection of additional (primary) data." The Draft Guidance describes one example, stating that "data collection in a non-interventional context when done according to a research protocol (e.g., for a registry) represents primary data collection." We suggest that FDA clarify whether different considerations apply when sponsors design non-interventional studies using primary data versus secondary data.

B. Considerations for Non-Interventional Studies

1. Overview

- In line 105, the Draft Guidance describes that "successful proposals" for non-interventional study designs should satisfactorily address study elements described in the Draft Guidance. We suggest that the Draft Guidance clarify that a "successful proposal" is a study proposal that is sufficiently detailed to receive constructive feedback and a favorable view from FDA on the adequacy of the study to meet specified goals for a regulatory submission. We also recommend that FDA provide representative examples of productive early engagement processes, including examples of non-interventional studies involving RWE used

[8] FDA, Guidance for Industry: Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products at 4 (2023).

to support the demonstration of substantial evidence of effectiveness in a pre-market application.

2. Summary of the Proposed Approach

- In lines 113–116, the Draft Guidance states that sponsors should "briefly summarize alternative study approaches and candidate data sources they considered before deciding on the proposed approach and discuss why alternative approaches . . . were not feasible in answering the specific study questions." We appreciate this recommendation and ask FDA to provide more information on the level of detail it hopes to reach in conversations related to alternative study approaches and candidate data sources so that sponsors can best prepare briefing books and related materials.

- In lines 133–36, the Draft Guidance states that sponsors should provide the results of any "preliminary or feasibility studies conducted to assess which data source is fit for use to address the research question being posed and to estimate the statistical precision of a potential study without evaluating outcomes for treatment arms." We ask that FDA clarify its recommendation that sponsors evaluate a data source for a particular use "without evaluating outcomes for treatment arms." It would be helpful to have insight into FDA's expectations on how sponsors can demonstrate that they followed FDA's recommendation.

3. Study Design

- We agree with the Draft Guidance that sponsors should describe strategies to address potential bias. For instance, the Draft Guidance explains that inferences drawn from non-interventional studies may be incorrect if based on estimates that are affected by forms of bias. Using real-world datasets that combine information from a variety of data sources can help to mitigate various types of bias. We suggest that FDA highlight the value of leveraging broad real-world datasets in a non-interventional study design and discuss any relevant considerations.

4. Data Sources

- We recommend that the Draft Guidance elaborate on the topic of primary data, such as by acknowledging the important role primary data can play as a component of RWE generation and by adding specific considerations that apply when non-interventional studies incorporate primary data.

- In lines 196–97, the Draft Guidance states that sponsors should describe "[a]vailable information on the timing of assessments for key data elements and completeness of these key data elements." We suggest that FDA revise this sentence to add "methods" and state, "Available information on the timing of assessment of key data elements, methods of assessment of these key data

elements (e.g., raw data from electronic medical record structured data versus curated data), and completeness of key data elements."

- In lines 204–05, the Draft Guidance states that sponsors should describe "[q]uality assurance activities that will be performed on the extracted original source data." We agree that quality assurance, along with documentation on any data transformations, is important. We suggest that FDA clarify which type of documentation will be sufficient for sponsors to demonstrate an understanding of quality assurance activities done on original source data.

5. Analytic Approach

- In line 240, the Draft Guidance states that the prespecified SAP should include information on its "[a]pproach to handling missing or misclassified data." We suggest that FDA revise this sentence to add the concept of identification and state, "Approach to identifying and handling missing or misclassified data."

- We suggest that FDA consider addressing the use of quantitative bias analyses. In some circumstances, quantitative bias analyses can help quantify the direction and magnitude of bias and provide helpful context for interpreting causal results from non-interventional studies.

The RWE Alliance appreciates the Agency's commitment to advancing the use of RWD and RWE in regulatory decision making. Thank you for considering these comments, and please let us know if you have any questions. We welcome the opportunity to discuss further.

Best regards,

The RWE Alliance