REAL-WORLD EVIDENCE ALLIANCE

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September 3, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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Re: M14 General Principles on Plan, Design, and Analysis of Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of Medicines; International Council for Harmonisation; Draft Guidance for Industry; Availability (Docket No. FDA-2024-D-2754)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to comment on the draft guidance titled "M14 General Principles on Plan, Design and Analysis of Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of Medicines" ("Draft Guidance").[1] We are a coalition of real-world data ("RWD") and analytics organizations with a common interest in harnessing the power of real-world evidence ("RWE")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

[1] 89 Fed. Reg. 55613 (July 5, 2024).

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

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]

We applaud FDA and the International Council for Harmonisation ("ICH") for developing a comprehensive and thorough set of recommendations for post-marketing safety studies that use 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 Section I of this letter provides general comments on the Draft Guidance and Section II provides specific comments on topics addressed in the Draft Guidance.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 and ICH for the approach taken in the Draft Guidance, which will help the RWE ecosystem continue to advance studies that utilize fit-for-purpose data for the safety assessment of medicines. FDA often acknowledges that RWD and RWE have long been utilized by regulatory authorities for post-market safety evaluation. We recommend acknowledging this historical use in the Draft Guidance to provide additional background and context on the value of RWD/E for post-market safety assessments.

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. Framework for Generating Adequate Evidence using Real-World Data

Figure 1 helpfully illustrates a framework for generating adequate evidence using fit-for-purpose RWD to address regulatory questions on the safety of medicines. Because the Draft Guidance covers each of the topics listed within Figure 1, we suggest adding corresponding section numbers to key topics within each box. For instance, Box 2 states "Define research question and key study design elements." We suggest adding "See 4.1 Research Question." This simple change would help readers navigate the Draft Guidance more effectively.

B. Feasibility Assessment(s)

- In lines 151–154, the Draft Guidance states that feasibility assessments should be structured in at least two phases: (1) an initial scan to determine whether data are available, likely sufficient, and to narrow down data source options; and (2) a subsequent, more comprehensive feasibility assessment of the candidate data sources. We suggest adding a phase at the outset, before the initial scan: developing a list of critical and optional data elements needed to answer the research question. FDA and ICH should also consider noting that sponsors

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

should consider identifying other key criteria at this stage, such as access to data, data use rights, partnership options, data lag and timeframe, and data restrictions such as de-identification.

- In lines 167–169, the Draft Guidance states that sponsors "should obtain any required third-party agreements to access relevant patient-level or analytic data that will be required by the regulatory authority for submission." We recommend defining key terms in the glossary, including "access," "patient-level data," and "analytic data," as a shared and consistent understanding of these terms will be critical for the agreements that FDA recommends.

- In lines 183–184, the Draft Guidance references identifying "a manageable number of available data sources" as potential candidates for utilization in the study. Because what is "manageable" is use-case specific and may differ across organizations, we recommend that the Draft Guidance replace "manageable" with "sufficient."

- In lines 213–216, the Draft Guidance highlights considerations for when a sponsor proposes a primary data collection study. We suggest that FDA and ICH add considerations for when sponsors leverage both primary and secondary data for a study, including considerations for data privacy, re-identification risk determinations, and the potential need for tokenization and separation of environments when linking data.

C. Protocol Development

The Draft Guidance states that the protocol should include a description of the expertise and credentials of the study team. We agree that protocol authorship and study execution should be driven by subject matter experts and pharmacoepidemiologic knowledge. However, the subject matter experts who write and author the protocol may differ from the study team. In addition, long-term study teams could be subject to change over time. As such, we recommend that the Draft Guidance recommend the protocol describe its authors and other accountable parties.

D. Data Sources

- In the subsection "Appropriateness of Data Sources in Addressing Safety Questions of Interest," we suggest including the structure of the data source (i.e., how data are captured in structured fields, unstructured notes, or other types of artifacts such as imaging and pathology reports) in the list of key aspects of the proposed data source.

- In the subsection "Characteristics of Major Data Sources," when discussing electronic health record (EHR) data, the Draft Guidance cautions that failure to capture additional data linkages (e.g., pharmacy records, history of medicine use, or medical care data on patients with certain types of privacy concerns) can result in inaccurate or incomplete data on healthcare delivery. However,

sometimes such data may be inaccessible or otherwise unobtainable. As such, we recommend that ICH remove the phrase "failure to capture," and instead state "The unavailability of these data can result in inaccurate or incomplete data." This would provide a description that better captures the range of situations that may arise.

- In the subsection "Characteristics of Major Data Sources," when discussing federated data networks (FDNs), the Draft Guidance provides a high-level description of FDNs that enable distributed analyses among multiple databases. Given the growing role of FDNs in the development of reliable and reusable RWD sources, we suggest adding best practices demonstrated by leading FDNs. We also recommend listing the following attributes of FDNs: (1) use of a common data model and guidelines to drive consistency in transforming data into a common format; (2) use of standard data quality reporting guidelines; (3) use of standardized ontology and terminology; (4) use of standardized, verified, and validated analytic methods, which may be adapted per use case; and (5) maintenance of a central coordinating center to facilitate and govern the FDN.

- In the subsection "Data Standardization," we appreciate that the Draft Guidance describes several challenges to data standardization in the context of FDNs and multi-database studies. We suggest referencing another potential challenge focused on ensuring that each data source is following the same standardization guideline(s). For instance, in the OMOP CDM standard, a patient record showing an injection of a drug should be transformed to both the drug-exposure and the procedure-occurrence tables. This allows the information about the drug and the physical procedure to be captured. Unless all data sources used in the study follow this guideline, the analysis would likely result in missing patients. As such, we recommend that FDA and ICH add a new paragraph after line 483 that states "Data standardization of RWD may generate incorrect results if the data source selected does not follow the same standardization guidelines. It is essential to perform verification and validation of the data standardization to ensure consistency between all data sources used in the study."

E. Selection Bias

The Draft Guidance states that "[d]ifferent forms of selection bias may be addressed in either the design (preferred) or analysis stages." We agree that selection bias can be addressed in both phases, but it is preferred to address selection bias in the design phase as it can be more difficult or impossible to address during analysis. As such, we recommend that FDA and ICH state that sponsors should address selection bias during the design phase.

III. Conclusion

The RWE Alliance appreciates the Agency's and ICH's commitment to advancing the use of 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