REAL-WORLD EVIDENCE ALLIANCE

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2024-N-5057: Public Workshop on Optimizing the Use of Real-World Evidence in Regulatory Decision-Making for Drugs and Biological Products-Looking Forward; Request for Comments

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to respond to the Request for Comments on the public workshop titled "Optimizing the Use of Real-World Evidence in Regulatory Decision-Making for Drugs and Biological Products—Looking Forward" (the "Request for Comments").[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. 89646 (Nov. 13, 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 for launching the Agency's new Center for RWE Innovation ("CCRI" or the "Center") focused on advancing, coordinating, and promoting consistency across RWD/E-related initiatives in CDER and across FDA. The Center's timely launch coincides with FDA reaching a major milestone by recently finalizing the core suite of RWE guidances directed by the 21st Century Cures Act. We strongly support FDA's ongoing work to build on the foundational RWE-related polices FDA has developed in recent years. The clinical research field is seeing rapid advances in the scientific methods and data infrastructure necessary for RWE-based research. At the same time, the larger ecosystem in which drug development occurs is transforming rapidly and requires innovative approaches, including the wider application of RWD/E, to generate robust evidence for regulatory decision making. RWD/E is foundational to the development and evaluation of artificial intelligence ("AI"), and FDA's progress developing policy on RWD/E provides an important foundation for the Agency's approach to AI.[4] The CCRI is well-positioned to serve as a focal point to develop policy on a range of innovative study design and evidence-generation approaches, and we look forward to working with the Center to advance the Agency's next generation of RWD/E policy.

Stakeholders at FDA's public workshop discussed key areas that have the potential to advance the generation and use of RWE for regulatory decision making. We offer our comments on this topic for FDA's consideration. For ease of reference, our comments respond to each question posed by FDA in the Agency's Federal Register notice.

In Response to Question #1: "Regulators, sponsors, and other interested parties are gaining experience with RWE in regulatory submissions. What are critical issues that need to be addressed to further advance the use of RWE in regulatory decision-making for drugs and biological products?"

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

[4] In a recent draft guidance, FDA describes the application of principles drawn from the Agency's approach to RWD/E—relevance and reliability—in the context data used to develop AI models. FDA, Draft Guidance for Industry and Other Interested Parties: Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products, at 4–5 (2025), https://www.fda.gov/media/184830/download ("[D]ata used to develop AI models should be *fit for use*, which means the data should be both relevant (e.g., includes key data elements and sufficient numbers of representative participants or sufficient data that is representative of the manufacturing process or operation) and reliable (i.e., accurate, complete, and traceable).").

A. Further Development of FDA's Approach to Reviewing Data Reliability

The RWE Alliance acknowledges FDA's efforts to describe how it evaluates the reliability of the data used to support regulatory decisions.[5] We believe this is a critical area for further development by FDA because understanding how to meet FDA expectations for data reliability is central to the design and implementation of studies using RWD. Sponsors and data organizations need to understand not only what standards FDA will apply to the review of data reliability but also how to provide relevant information to FDA to support FDA's review.

While these topics are addressed in recent FDA guidance documents, the level of detail provided by FDA is often insufficient to provide confidence to stakeholders about whether FDA would find a data source or data collection method to have an acceptable level of reliability or how to provide relevant information to FDA. For example, FDA's final guidance "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products" leaves some confusion and uncertainty about how and under what circumstances the Agency might require submission of patient-level data or access to original source data upon FDA inspection.[6] An overly broad approach to accessing source data or a policy that remains unclear on this point could have a chilling effect on what data are available for research.

We recommend that FDA consider a variety of approaches that may enable FDA's review of the reliability of data sources and that can facilitate the process of providing information to FDA to support this review. For example, FDA should consider (1) the development of standardized methods to provide sufficiently detailed traceability and lineage documentation for RWD sources; (2) access to datasets in a manner that limits use and disclosure of sensitive, identifiable information; and (3) mechanisms for FDA to leverage an earlier evaluation of reliability for an RWD source that may be utilized in multiple studies or included in multiple submissions—coupled with a process for communicating that review to sponsors that are considering use of a data source in a submission.

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[5] *See, e.g.*, FDA, Guidance for Industry: Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products, at 3 (2023), https://www.fda.gov/media/152503/download ("[T]he term reliability includes accuracy, completeness, and traceability.").

[6] 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 6 (2023), https://www.fda.gov/media/171667/download ("Sponsors must ensure that they are able to submit patient-level data for any RWD that have been analyzed as part of the clinical study included in a marketing application when required under 21 CFR 314.50 and 601.2. . . . and that source data necessary to verify the RWD are made available for inspection as applicable.").

FDA also should resolve questions that may arise about the ability of sponsors or data providers to provide certain RWD to FDA in a manner that is consistent with upstream, privacy-related limitations. For example, even when identifiers have been removed from a dataset, there are situations where providing FDA access to patient-level RWD may pose a challenge under HIPAA or other privacy frameworks. We offer several actions for FDA's consideration that may help to address uncertainties in this area. First, FDA should publish a statement of existing data protections to clarify safeguards under current law, regulations, and Agency practice that protect the confidentiality of sensitive data sets. Second, FDA should explore the feasibility of alternatives to the exchange and transfer of patient-level RWD via alternate modes of access. Third, FDA and stakeholders in the RWE ecosystem should identify any regulatory or statutory changes that may be needed to clarify FDA's ability to accept data that is subject to upstream limitations.

We also believe that FDA should continue to clarify its expectations for RWD submissions through clearer language and terminology to describe key terms and concepts regarding the exchange and transfer information to FDA to support FDA's review of data reliability. Where possible, we urge FDA to define key terms; align on language and terminology across documents; and clarify how patient-level data submission expectations may depend on the type of study, data source, or role in FDA decision making. We recommend that FDA explain how FDA determines submission expectations for studies involving RWD. Clear expectations on FDA's concepts and terms for data reliability will help to provide a basis for sponsors, research organizations, and data sources to collaborate on data-sharing approaches that maximize the availability of RWD for submission to FDA.

We encourage FDA to adopt a consistent approach utilized across the Agency for access to patient-level data and source data review, including with training of the FDA staff involved. Development by FDA of clearer and more specific regulatory expectations on data reliability for RWE submissions will help the ecosystem maximize the potential value of RWE in FDA's regulatory decision making—ultimately benefiting patients.

B. Artificial Intelligence and RWD

The use of RWD in the development and deployment of AI technologies in the healthcare and life sciences sectors has the potential to yield enormous benefits. AI tools are rapidly expanding the types of RWD that can be collected and the methods for that collection, as well as the ability to evaluate data and data quality. High-quality, reliable, and representative RWD will play a critical role in the training, validation, and monitoring of AI systems in healthcare and medical product development.

Of relevance to this Request for Comments, we believe that there are important intersections between RWD/E and AI for FDA to continue to consider from a regulatory science and policy perspective as it develops AI-related policies. For example, the data used to develop and train AI models can come from a variety of RWD sources, and AI

technologies have increasing importance in the collection and analysis of RWD. We acknowledge FDA's recent guidance on AI in regulatory decision making for drugs and biologics[7]—in addition to the Agency's development of AI-related guidance in the medical device context—and look forward to opportunities for experts from the RWE ecosystem, both within and outside the Agency, to inform FDA's important work in this area.[8]

C. Transparency in FDA Review of RWD/E Submissions

The RWE ecosystem will be better equipped to use RWE in clinical trial designs with more transparency on the role of RWE in FDA's regulatory decisions and on the ways that FDA reviewers judge the use of RWD/E in various applications. We offer three recommendations to increase public disclosure of FDA's review of RWD/E in submissions.

First, we recommend that FDA include a dedicated section in its Integrated Review summarizing the RWD/E submitted and reviewed as part of an original or supplemental drug product marketing application. FDA should address any analyses of RWD, whether previously published or unpublished, that are conducted by the sponsor or an external party and are intended to support the assessment of clinical effectiveness or safety. FDA should state how FDA considered the RWD/E as part of the marketing application, including with respect to the Agency's risk-benefit assessment that informs regulatory decision making. At a minimum, FDA should describe for each study involving RWD that is considered in FDA's review of a marketing application the following:

> (1) the source and type of RWD;
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> (2) FDA's evaluation of the study design and analysis methods, including information about how RWD contributed to the study (this could consider, e.g., data for endpoint assessment, data for an external control arm, safety data necessary for an NDA/BLA approval or to satisfy a postmarketing requirement or commitment, or other uses of RWD); and

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[7] FDA, Draft Guidance for Industry and Other Interested Parties: Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products (2025), https://www.fda.gov/media/184830/download.

[8] Comment from RWE Alliance, Discussion Paper: Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products, Docket No. FDA-2023-N-0743-0054 (Aug. 9, 2023), https://www.regulations.gov/comment/FDA-2023-N-0743-0054.

(3) the role of the study involving RWD in FDA's review of the application (e.g., whether the study contributed to substantial evidence of effectiveness, evidence of safety, or other contextual or supportive evidence).[9]

We also encourage FDA to help the RWE ecosystem better understand how FDA reviewers evaluate studies involving RWD/E in medical product regulatory applications, including by providing feedback to sponsors and third parties on whether the RWD are fit-for-purpose in specific study submissions. We suggest that FDA include a description of the Agency's engagement with the sponsor on the real-world study design. Adding a dedicated section for RWD/E also may facilitate greater consistency among FDA reviewers and review divisions in their assessment of RWD/E in marketing applications.

Second, we appreciate that the Center for Devices and Radiological Health released representative examples of RWE used in medical device regulatory decisions, including file summaries, RWD sources, populations, and descriptions of use. We encourage FDA's drug and biological product review divisions to take similar action. FDA could (1) create a centralized and public RWE Program "dashboard" on FDA's website; (2) publish periodically a report that summarizes actual use cases; and (3) publish aggregate information on the Agency's observations about RWE studies that have and have not met regulatory expectations, to the extent permissible under FDA's information disclosure laws.

Third, we commend the Agency for recently publishing its report on CDER and CBER submissions containing RWE, consistent with its PDUFA VII commitment. As FDA explained, its report captures only certain RWE submissions. It does not cover submissions containing RWE that provide supportive evidence or contextualize safety information. We encourage FDA to continue publishing information about RWE submissions and, in the future, expand the scope to provide even more information about how RWE is being used in submissions.

These steps are crucial for advancing best practices within the RWE ecosystem and for spreading awareness of the benefits that RWE ultimately delivers to patients. We encourage FDA to continue to engage with the RWE ecosystem to identify other information on RWD/E or innovative clinical development approaches that would help ensure stakeholders understand how FDA considers RWD/E in the regulatory decision making process.

D. Innovative Trial Designs

FDA has long recognized the value that RWD/E can bring to many different aspects of clinical trials—both to inform the design and operation of a clinical trial and to serve as a

[9] The Alliance believes FDA can provide useful details in each of these areas, while ensuring appropriate protections for trade secret and confidential commercial information.

data source for a clinical trial itself.[10] For instance, a randomized clinical trial can use RWD to capture clinical outcomes or safety data, including through pragmatic and large simple trials. RWD also can play a role in a decentralized clinical trial program, such as "real life" data collected from wearables or data obtained from routine clinical care settings. External control arms, including synthetic control arms, can offer an important tool for generating evidence on safety and effectiveness.

These examples highlight the diversity of ways in which RWD can be used to enhance the design and conduct of clinical trials, further demonstrating that RWD sources are an important component of innovation spanning all trial designs. FDA should continue to collaborate with the RWE ecosystem to identify opportunities to use RWD across a range of clinical trial designs and contexts. We also encourage FDA to provide concrete recommendations to address trial design, data source and access, data analysis, and methodological challenges that sponsors may face when designing innovative clinical trials using RWD.

In Response to Question #2: "To advance our understanding of RWE, FDA has funded various demonstration (research) projects on topics such as RWD sources, study designs, and specific 'tools.' What research priorities, including emerging technologies and AI, should CDER consider supporting?"

We believe FDA should have a prominent role in supporting research that aims to improve RWE-related infrastructure, technologies, and methodologies. One area of research where FDA involvement will be particularly important is research and demonstration projects that inform FDA's approach to the assessment of data reliability for data that are used to support different types of regulatory decision making, including by contributing to substantial evidence of effectiveness. Specifically, additional research on this topic could focus on data quality attributes that sponsors and data providers should capture, evaluate, and share with FDA to support FDA's review of data reliability for a particular data source.

For instance, research on methods to document data provenance could help the RWE ecosystem develop new and enhanced documentation methods (e.g., on data accrual, data cleaning, data validations, data transformations, and data linkages) to facilitate FDA's review of an RWD source. We believe it is essential for FDA also to collaborate with other agencies, including the Assistant Secretary for Technology Policy/Office of the National Coordinator for Health Information Technology, and stakeholders to develop and implement data standards that are optimized for modern data collection and analysis methods and that can support the use of RWD/E in FDA's regulatory decision making. FDA should inform its work in this area through research and demonstration projects, as needed. We encourage research that provides examination

[10] FDA, Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products, at 3 (2023), https://www.fda.gov/media/171667/download.

of and is applicable across multiple use cases, including scenarios with a variety of data sources, such as electronic health records, claims data, and registries, and a variety of linkage and aggregation approaches. Research should include use cases that incorporate data on patient-reported outcomes and from different clinical settings. FDA also should continue to report findings from research that the Agency has supported previously, including findings relevant to its policy recommendations in guidance.

In Response to Question #3: "FDA has published RWD/RWE guidance documents focused on data considerations, study design, and regulatory considerations. What additional topics could be prioritized for consideration?"

We acknowledge the substantial efforts of FDA to issue guidance on RWD/E topics over the past few years. As we note above, the types of data sources, innovative trial designs using those data sources, methods to generate RWD/E, and availability of data standards that are optimized for RWD/E continue to evolve rapidly. We encourage FDA to develop and implement a plan for updating, as needed, the Agency's existing draft and final guidances on RWD/E to reflect these scientific and technological advancements. We also note the importance of RWD/E-related issues in the context of AI and encourage FDA to continue working with stakeholders to develop guidance on scientific and policy issues at the intersection of these two important topics.

In Response to Question #4: "FDA has utilized various mechanisms (e.g., public meetings, webinars, 'listening sessions') to engage interested parties; the Agency has also facilitated discussions with international regulators. What are optimal communication and engagement strategies to interact with the external community regarding RWE?"

We appreciate FDA engaging with the RWE ecosystem in a variety of settings. We encourage FDA to continue hosting workshops, public meetings, listening sessions, and other forms of public engagement with the goal of informing FDA policies on RWD/E.

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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