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: Enhancing Adoption of Innovative Clinical Trial Approaches; Public Workshop; Request for Comments (Docket No. FDA-2023-N-4489)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to respond to the Request for Comments on the Public Workshop "Enhancing Adoption of Innovative Clinical Trial Approaches" ("Workshop"). 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.[1]

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.[2]

We agree with FDA (the "Agency") that the ecosystem in which drug development occurs is rapidly transforming and, further, that this transformation requires innovative trial strategies, including "wider application in regulatory drug development of real-world

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

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

data sources."[3] We believe that the use of real-world data sources in clinical trial designs can add value and efficiencies to drug development and further spur the development of promising new therapies to benefit patients. We offer the following specific comments for FDA to consider discussing at the upcoming Workshop.

I. Value of RWD/E in Drug Development and Clinical Trials

The use of fit-for-purpose RWD should be leveraged wherever possible for medical product innovation and regulatory decision making. We recommend that FDA highlight the value that the use of RWD can bring to drug development, evidence generation, and the regulatory decision-making process, such as by helping to (1) provide additional insights on the safety and effectiveness of medical products in real-world settings, (2) better understand treatment effects in underrepresented populations, (3) generate evidence of effectiveness for serious conditions with significant public health needs or for rare disease indications with small patient populations that cannot be studied using a randomized design, and (4) increase efficiency in generating the clinical evidence needed to support regulatory decisions.

We also recommend that FDA highlight the potential uses of RWD/E in a variety of clinical trial designs. FDA has long recognized the value that RWD/E can bring to many different aspects of interventional clinical trials—both to inform the design and operation of a clinical trial and to serve as a data source for a clinical trial itself.[4] 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 from routine clinical care settings. External control arms, to include synthetic control arms, can also offer an important alternative for generating effectiveness evidence for serious conditions, as noted above. In addition, clinical trials or observational studies can use RWE to fulfill a post-marketing requirement or commitment to further evaluate safety or effectiveness and support a regulatory decision. Observational studies also can generate RWE intended to help support an efficacy supplement. These examples highlight the diversity of ways in which RWD can be used to enhance the design and conduct clinical trials, further demonstrating that real-world data sources are an important component of innovation spanning all trial designs.

The potential use of RWD in any trial design depends on the fitness of the RWD in question for the particular purpose. The potential uses of RWD for innovative clinical trials are broad and increasing because the clinical research community is rapidly expanding the types of RWD that may be collected; methods for that collection; and

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[3] FDA, Enhancing Adoption of Innovative Clinical Trial Approaches; Public Workshop; Request for Comments, Docket No. FDA-2023-N-4489, https://www.regulations.gov/document/FDA-2023-N-4489-0001.

[4] 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).

ability to evaluate, control, and document critical data attributes that determine "fitness," such as data quality, including through the use of Artificial Intelligence and Machine Learning. For some potential trial uses, collection of RWD (e.g., from an EHR) may need to be planned ahead of the trial, prospectively, to control quality. For other uses, analysis of available datasets is appropriate, but there may be a need to develop and validate analytical approaches to ensure fitness. These nuances point both to the wide potential uses of RWD in clinical trials, and also to the opportunity for FDA to work collaboratively with the RWE ecosystem to discuss and refine the methods for using RWD in innovative trials intended to support regulatory decision making.

At the public workshop, we encourage FDA to call attention to the ability of fit-for-purpose RWD/E to examine a variety of research questions within various innovative trial designs. RWD/E can be agile in evidence generation by integrating diverse data sources, thus ensuring a comprehensive and nuanced understanding of the real-world impact of therapeutic interventions across subpopulations. RWD also allows for direct ingestion of patient-generated data such as biometric data, survey data, and symptom diaries, among others. Leveraging RWD for clinical trial designs also can accelerate medical product innovation by increasing the efficiency of trial accruals and ultimately more rapid, successful completion of clinical trials. RWD/E that is fit-for-purpose in any clinical trial design can and should be used as a potential source of supportive, confirmatory, and substantial evidence in regulatory decision making.

II. Barriers to the Use of RWD/E

The RWE Alliance supports FDA's efforts to develop and implement policies to ensure the RWD/E used in regulatory decision making are transparent, auditable, reproducible, and scientifically valid. To realize the full potential of RWE in all types of clinical trial designs and benefit patients, FDA should apply its policies in a manner that accounts for the unique considerations of RWD/E and address challenges and barriers that may curtail use of RWD.

A. Access to Data and Source Records

We agree with Dr. Califf's recent FDA Voices post that a key challenge in the use of RWE for regulatory decision making "involves safeguarding patient privacy while having suitable mechanisms for data access and inspection by regulatory agencies."[5] The RWE Alliance understands and appreciates FDA's need to have confidence in the quality and integrity of source data and to have patient-level data submitted to the Agency when a clinical trial using RWD/E is used as substantial evidence to support regulatory approval. At the same time, in the absence of more detailed information about FDA's expectations around access to source data when sponsors use RWD/E in trials for substantial evidence, as well as around acceptable approaches that can be leveraged to meet those expectations in the context of RWD, FDA's high-level reference

[5] Dr. Robert M. Califf, *Realizing the Promise of Real-World Evidence* (Dec. 21, 2023), https://www.fda.gov/news-events/fda-voices/realizing-promise-real-world-evidence.

to needing “access” to secondary data sources could have the unintended consequence of chilling use of valuable RWD.

We appreciate that FDA notes in its final guidance “Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products” that there may be circumstances in which a sponsor cannot submit patient-level data to FDA through traditional channels. Moreover, FDA recognizes that sponsors may not always own or control relevant RWD, yet must ensure such RWD are available for inspection by FDA. FDA’s guidance still leaves some confusion and uncertainty about when and how the Agency might require access to original source data and records upon inspection and what that access will look like in practice. We support Dr. Califf’s statement about the need for FDA to collaborate with the RWE ecosystem to advance FDA’s objectives and expectations in a manner that accounts for the unique legal and regulatory considerations associated with real-world data sources. We also recommend that FDA 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. FDA should consider identifying circumstances in which it is appropriate for FDA to validate the methodologies used on a data set to confirm data reliability and integrity instead of reviewing source data directly. For instance, FDA should clarify that its expectations on accessing source data may vary depending on the context of the use of the RWE.

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. For example, hospitals, clinics, or providers with fewer resources may opt out of making data available for research if they have concerns about their capacity to accommodate potential FDA inspections or related regulatory requirements. This could have a disproportionate impact on smaller systems or community-based providers, and, as such, the representation of minorities and other under-represented communities may be diminished in real-world research. We believe that these impacts must be avoided and that RWD/E should be available from more communities to enhance clinical trial designs and for FDA regulatory decision making.

We appreciate Dr. Califf’s acknowledgement that FDA will work to address challenges with continued collaboration between the Agency and stakeholders. The RWE Alliance remains committed to working with FDA as the Agency advances policies on access to source data to meet FDA’s objectives and expectations. We are encouraged by the potential of future collaboration to help identify a path forward and realize the full potential of RWD/E to ultimately benefit patients.

B. Application of Existing Regulations

We believe that regulatory expectations for studies involving RWD/E should be tailored to the unique advantages and considerations presented by RWD/E. RWD differ from traditional clinical trial data in how and why they are collected, curated, and analyzed. Due to these distinctions, RWD can have some important differences when compared with clinical trial data, while also offering unique advantages for drug development,

evidence generation, and regulatory decision making, as discussed above. For example, RWD may be aggregated as a multipurpose dataset that can provide insights for specific products that would not be apparent in clinical trial data. As use of RWD/E in regulatory decision making continues to expand, flexibility in how FDA applies policies that were developed largely focused on traditional clinical trials will be important to ensure that studies involving RWD/E further evolve with innovation in drug development.

We appreciate that FDA released the final rule "Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations," which explains that some RWD study designs could fall under the definition of "minimal risk" and thus permit an Institutional Review Board ("IRB") waiver or alteration of informed consent on a case-by-case basis. We agree with FDA's two examples for which FDA would anticipate that sponsors request a waiver or alteration of informed consent (i.e., research involving previously collected data and biospecimens, certain studies involving FDA-approved or cleared products). That said, FDA did not specify that certain categories of minimal risk investigations would necessarily qualify for a waiver, which may lead to uncertainty as IRBs make decisions on a case-by-case basis. We welcome additional clarity on other types of studies involving RWD/E that would qualify for an exemption or waiver.

In addition, the RWE Alliance commented on these topics as part of its response to the December 2021 draft "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Guidance for Industry."[6] Because FDA's final "Considerations" guidance still left some open questions about the application of existing regulations to studies involving RWD/E, we reiterate our points below and encourage FDA to use its upcoming Workshop to provide additional clarity. First, FDA should provide more specific examples or a flow chart (via a vehicle like a Q&A document) of RWE studies and whether FDA views those example studies as subject to parts 50, 56 and 312. We recommend FDA better clarify when it views an RWE study as a "clinical investigation" subject to part 312 and how FDA intends the definitions of interventional and non-interventional studies to intersect with the scope and applicability provisions of parts 50, 56, and 312. Second, FDA should address inconsistencies in how its regulations are currently implemented. For example, IRBs are often inconsistent in their application of Good Clinical Practice regulations to RWD studies, such as in hybrid studies that combine non-interventional and interventional elements in the study design (e.g., pragmatic randomized trials).

Generally, we recommend that FDA incorporate flexibility to account for and inform on a wide range of ways in which RWD/E can be used in the regulatory process, coupled with opportunities for scientific discussion with FDA reviewers of trial-specific data considerations. In addition, we recommend FDA consider innovative methods, such as

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[6] RWE Alliance, Comments on Draft Guidance on Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Guidance for Industry, Docket No. FDA-2021-D-1214-0023 (Mar. 9, 2022).

early informed consent approaches, when appropriate, that could further facilitate leveraging RWD for regulatory purposes. We are confident that the use of RWE can be considered and accepted by FDA in a way that reflects both these advantages and unique considerations presented by studies involving RWD/E, without compromising the quality of the evidence used for regulatory decision making.

C. Design Considerations

FDA should continue to collaborate with the RWE ecosystem to identify solutions to potential design challenges when using RWD across clinical trial designs. For example, FDA has identified trial design, data source and access, data analysis, and methodological challenges that sponsors may face when designing innovative clinical trials, including externally controlled trials and external control arms, using RWD. We recommend that FDA provide concrete recommendations to address these barriers and also highlight use cases that demonstrate innovative trial designs in which RWD has been used by FDA in regulatory decision making. We also welcome FDA inviting stakeholders in the RWE ecosystem to share perspectives on ways to operationalize FDA's recommendations.

D. Data Standards

FDA has an essential role in driving the development of standards through projects like USCDI+, which can facilitate the generation of RWD that is fit for use in trials to support regulatory decision making. FDA participation in data standards efforts is also an important opportunity for FDA to gain experience with the benefits and shortcomings of emerging data standards. This experience will help the Agency focus its resources on advancing the science of RWD use in innovative clinical trials.

E. Transparency in FDA Review of RWD/E

The RWE Alliance commends FDA for its guidance "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products," and we will continue to promote this guidance within the RWE ecosystem to help ensure that stakeholders have better public records on the use of RWD/E in medical product applications and can better understand how FDA reviewers consider RWE in the regulatory decision-making process. We likewise support FDA's promotion of this guidance document to help encourage sponsors' use of it.

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. There is an information gap on how various innovations, including the use of RWD/E, impact FDA decision making as it pertains to New Drug Applications, Biologics License Applications, and supplemental applications to expand a current label. FDA is best situated to address this gap. For example, we support FDA making public a summary of the Agency's review of RWE when included in original or supplemental applications. We also encourage that FDA

include in review documents a brief statement about the use of RWD/E considered as part of the medical product application.

We commend the Center for Devices and Radiological Health for releasing a representative example 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. With more transparency, including through public disclosure of how FDA reviewers judge the use of RWD/E in various applications, the RWE ecosystem will be better equipped to use RWE in clinical trial designs.

III. Conclusion

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