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Re: Use of Real-World Evidence To Support Regulatory Decision-Making for Medical Devices, Draft Guidance for Industry and Food and Drug Administration Staff; Availability (Docket No. FDA-2023-D-4395)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to comment on the draft guidance titled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" ("Draft Guidance").[1] We are a coalition of real-world data ("RWD") and analytics organizations with a common interest in harnessing the power of real-world evidence ("RWE")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] 88 Fed. Reg. 87,782 (December 19, 2023).

[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 applaud the Center for Devices and Radiological Health ("CDRH") and Center for Biologics Evaluation and Research ("CBER") for releasing a Draft Guidance that extols the role and value of RWD/E in informing FDA's (the "Agency's") understanding of the benefit-risk profile of devices to the benefit of patients. Section I of this letter provides our general comments on the Draft Guidance and Section II highlights comments on specific regulatory topics discussed in the Draft Guidance.

I. General Comments on the Draft Guidance

As noted above, the RWE Alliance believes that the Agency's clear and consistent communication about the Agency's use of RWE is crucial to advancing best practices in the use of RWE for regulatory purposes and to ensuring widespread understanding of the benefits that RWE ultimately delivers to patients. We therefore appreciate that the Draft Guidance provides a series of representative examples demonstrating FDA's facility with RWE for device-related decision making and the real-world acceptability of RWE to inform and support regulatory uses. We also applaud CDRH for publishing "Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions," and we encourage CDRH to issue additional reports in the future.

In the recent Draft Guidance, we also commend FDA for building on its earlier 2017 guidance by providing significantly greater depth and clarity around assessing the relevance and reliability of RWD for a broad series of device-specific use cases. For instance, the level of detail and specifics around how to achieve acceptability of RWD are notable, such as in the details on study time and index date, as well as expectations for conceptual and operational definitions. The Draft Guidance lays out clear expectations of what is expected from the fit-for-purpose assessment (Section V of the Draft Guidance) and other study documentation (Appendix A) that can provide stakeholders with practical steps that need to be incorporated from design to submission. The Draft Guidance section on RWD from devices authorized for emergency use is also helpful in describing the potential ways to leverage RWD for decision making when the device is being used within the scope of its authorization.

We appreciate the policies and approaches outlined in the Draft Guidance, as they underscore that FDA understands the value and opportunities—as well as the complexities and challenges—that come with using RWD. For example, we appreciate that the Draft Guidance acknowledges that sponsors may not always have access to participant-level data or the RWD source, and for describing how sponsors can still ensure database quality. We believe that the Draft Guidance provides a clear pathway for the sponsor and FDA to evaluate and understand the RWD without compromising the quality of the evidence used for regulatory decision making or introducing legal or ethical barriers to protecting patient privacy.

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 titles used in the Draft Guidance.

A. Regulatory Context in Which Use of RWE May be Appropriate

1. General Considerations for the Use of RWE

- In Section IV.A, footnote 15 states, "Generally, FDA does not consider published literature to be RWD." FDA's position implies that published literature generally will not be considered RWD regardless of the data described in the published literature. We ask that FDA clarify this statement, including FDA's approach to published literature that describes evidence derived from RWD, and how sponsors should consider and present the underlying data referenced in the published literature in order for it be considered RWD.

- In Section IV.A, lines 232–33, FDA states that RWD may potentially be applicable as "a mechanism for re-training artificial intelligence/machine learning-enabled medical devices." We suggest that FDA instead state, "a mechanism for training, ongoing monitoring, and re-training artificial intelligence/machine learning-enabled medical devices."

B. Assessing Data Relevance and Reliability

- In Section V, lines 342–44, the Draft Guidance addresses, at a high level, cases in which RWD are derived from multiple RWD sources. Over time, we expect an increasing number of studies intended for submission to CDRH to incorporate RWD from multiple sources, often in combination with data that are collected specifically for study purposes (e.g., by study site staff). For example, a study conducted at multiple sites may need to incorporate RWD from multiple electronic health record sources. Another example is a study that ascertains certain study variables using an algorithm that combines multiple sources (as discussed in Section VI.B of the Draft Guidance). For submissions that involve multiple data sources, we suggest that FDA clarify how the evaluation of relevance and reliability should be structured in the submission documents.

1. Relevance

- In Section V.A.1, lines 389–91, we appreciate and support FDA highlighting the use of the unique device identifier ("UDI"). We note that if the RWD does not capture the UDI, alternative methodologies may be used to identify exposure to a particular device, including, for example, by using ICD procedure codes; Current Procedural Terminology ("CPT") and/or Healthcare Common Procedure Coding System ("HCPCS") codes; Natural Language Processing ("NLP") algorithms; or

other identifiers such as catalog numbers, lot numbers, and product brand names. As such, we recommend that FDA update lines 389–91 to state, "Where appropriate, RWD sources containing device identifier (DI) portion of the unique device identifier (UDI) within the RWD set should be prioritized to support robustness of the device identification. If UDI is not available within a particular RWD source, validated alternative methodologies (e.g., CPT and/or HCPCS codes, ICD procedure codes, or NLP algorithms) or other identifiers (e.g., catalog numbers, lot numbers, or product brand names) may be considered to determine exposure to a particular device."

- In Section V.A.2, lines 421–22, we recommend that FDA clarify the type of regulatory submission (e.g., study protocol) in which sponsors should provide a description of their assessment of linkages.

- In Section V.A.4, lines 453–59, we suggest that the Draft Guidance clarify the difference between "specified indication" and the "target population with the condition of interest." For generalizability purposes, sponsors should consider whether the study sample within a RWD source represents the larger target population of patients with the specific indication of interest. As written, the Draft Guidance could be read to imply that the generalizability of the evidence will need to be demonstrated beyond the intended use population for which a sponsor is seeking approval/clearance or marketing authorization.

2. Reliability

- In Section V.B.2, lines 607–22, FDA acknowledges that participant-level data may not always be available to sponsors but notes the potential for sharing participant-level data with FDA. We commend FDA for its recognition that sponsors' access rights may be limited in some circumstances and suggest that FDA explicitly acknowledge the applicability of data privacy and protection regulations to the dissemination of participant-level RWD.

- In Section V.B.2, line 626, FDA states that sponsors should consider "[p]rior demonstration of RWE generation from the data source." We suggest that FDA add "as applicable" to the end of this sentence. Because novel data sources may be used to generate RWE for the first time, adding "as applicable" allows flexibility in situations where prior demonstration of RWE generation may not be relevant. Similarly, we recommend that FDA remove reference to "any" and "all" in Table 2, line 1025, which currently states, "Provide documentation of any previous RWD source fit-for-purpose assessment for a similar target population and all peer reviewed literature of RWE generation from data source."

C. Considerations for Methodologies for Collection and Analysis of RWD to Generate RWE

1. Methods for Study Designs Using RWD

- In Section VI.A, footnote 40 implies that "device utilization, participant characteristics, natural history of disease or disease trajectory, treatment environment and treatment patterns, as well as background rates of outcomes"[4] represent uses of RWD that do not constitute RWE. We ask that FDA clarify its language in the footnote to explicitly state whether FDA will consider these RWE and, if not, what practical implications follow from this classification.

2. Defining Study Design Elements

- In Section VI.B.1, lines 712–56, we suggest that FDA cross reference external resources[5] for further information on suitable study design visualizations. We believe that such information will be useful for sponsors less familiar with the production of visual depictions.

- In Section VI.B.1, lines 752–56, the Draft Guidance notes that the calendar time allotted for a study should be long enough to measure all data elements, from the beginning of the baseline period through the end of the follow-up. We suggest that the Draft Guidance characterize the time period to also include the time needed for data management, to conduct statistical analyses, and to prepare the final study report.

- In Section VI.B.2, FDA provides helpful information illustrating the opportunity to develop complex and robust conceptual and operational definitions for study variables. We encourage FDA to reference the regulatory submissions in which sponsors should include the conceptual definition (i.e., the study protocol) and those in which sponsors should include the operational definition (i.e., statistical analysis plan). We also encourage FDA to continue developing and refining guidance on this topic as FDA gains more experience reviewing submissions with these features.

- In Section VI.B.2, lines 824–32, the Draft Guidance provides one example of how sponsors can check for misclassification. The Draft Guidances then states, "Further exploration is recommended for data elements that are not aligned with expectation." FDA should consider providing additional details on the additional steps sponsors should take.

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[4] Draft Guidance, Lines 682–84.

[5] We recommend that FDA reference Schneeweiss S, et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med. 2019 Mar 19;170(6):398-406. DOI: 10.7326/M18-3079; Gatto N, et al. Visualizations Throughout Pharmacoepidemiology Study Planning, Implementation, and Reporting. Pharmacoepidemiol Drug Saf. 2022 Nov;31(11):1140-1152. https://doi.org/10.1002/pds.5529.

- In Section VI.B.3, lines 867–73, we suggest that FDA cross reference external resources[6] for further information on the logic and construct of causality diagrams. As noted above, we believe that such information will be useful for sponsors less familiar with the use of such methods.

D. Documentation for FDA Review

1. Protocol

- In Section VII.C, we ask that the Draft Guidance clarify if and when FDA review of an RWD study protocol is needed prior to conducting a premarket study involving RWD. In addition, if an Investigational Device Exemption is not required for the type of study, we ask that FDA clarify the mechanism sponsors should use to receive FDA feedback and approval for the proposed premarket study involving RWD.

- In Section VII.C, lines 935–37, FDA states that "individuals generating summary scores (e.g., propensity score modeling) should not have access to the outcomes within the dataset(s) used for the study." We recommend that FDA clarify whether this sentence is referring to publications[7] on the two-stage outcome-free design. In addition, we ask that FDA clarify whether sponsors should limit access to the outcomes within the dataset(s) only for the purposes of summary scores, when there may be other situations where access to linked treatment and outcome data should also be limited (e.g., exploring the data to confirm level of missingness).

E. Appendix A, Table 1

- The first row states, "Determine RWD source contains sufficient detail to capture data elements and address the study question." We recommend that FDA revise it to state, "Determine if the RWD source contains sufficient information to assess if the RWD source captures the needed (relevant) data elements to address the study question."

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[6] We recommend that FDA reference Greenland S, Pearl J, Robins JM. Causal Diagrams for Epidemiologic Research. Epidemiology. 1999 Jan;10(1):37-48. https://pubmed.ncbi.nlm.nih.gov/9888278/.

[7] Yue LQ. Statistical and Regulatory Issues with the Application of Propensity Score Analysis to Nonrandomized Medical Device Clinical Studies. J Biopharm Stat. 2007;17(1):1-13. DOI: 10.1080/10543400601044691; Yue LQ, Lu N, Xu Y. Designing Premarket Observational Comparative Studies Using Existing Data as Controls: Challenges and Opportunities. J Biopharm Stat. 2014;24(5):994-1010. DOI: 10.1080/10543406.2014.926367; Li H, et al. A Note on Good Practice of Objective Propensity Score Design for Premarket Nonrandomized Medical Device Studies with an Example. Stat Biopharm Res. 2016;8(3):282-286. DOI: 10.1080/19466315.2016.1148071.

- The fourth row states, “Ensure reasonable time between data collection and release for research.” We recommend that FDA revise it to state, “Assess the time lag between data capture and data availability for research. RWD sources with reasonable time between data collection and release should be used for studies that may support a regulatory submission.”

- In the fifth row, FDA uses “x” marks in both columns to indicate that the item “Consider changes in clinical practice/guidelines over time” is information that sponsors should both document and provide to FDA in submission. In other rows where both columns are marked with an “x,” FDA uses parentheticals to indicate that the item should be either “(detailed)” or “(high level).” We ask FDA to clarify whether FDA intended to include parentheticals by the “x” marks for this item.

- The last row states, “Ensure study sample is representative and generalizable to RWD source and target population.” We recommend that FDA focus on the target population only by removing the words “RWD source and.”

F. Appendix B

- In Appendix B, we appreciate that in Example 1, the Draft Guidance includes a statement about how the RWD might be considered reasonable (i.e., “[s]hould a manufacturer wish to expand indications, this type of RWD might be used”). FDA should consider including a similar statement that describes how RWD may be used or considered for other examples in Appendix B.

- In the 2017 guidance, “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices,” FDA included specific examples related to (1) post-approval device surveillance as a condition of approval and (2) objective performance criteria and performance goals, including the rationale for the use of RWD. In this Draft Guidance, Appendix B does not include these examples. We recommend that FDA re-insert these examples to demonstrate the breadth of applicable uses of RWE.

The RWE Alliance appreciates FDA’s commitment to 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