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RE: FDA-2023-D-4395: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Guidance for Industry

Thank you for the opportunity to respond to the U.S. Food and Drug Administration's (FDA) request for public comment on the agency's new draft guidance on the evaluation of real-world data (RWD) to determine whether they are of sufficient quality for generating real-world evidence (RWE) for regulatory decision-making in medical devices, which proposes recommendations that expand upon the 2017 finalized guidance. We, the undersigned, appreciate the efforts being made by the FDA to strengthen and modernize the continuing efforts to advance the use of real-world data in regulatory decision-making, focusing on the role of real-world evidence in the context of medical devices. This updated draft guidance takes important steps to ensure that guidance is offered broadly for sponsors for medical devices, and that the agency is confirming their stance on the role of RWD and RWE to support regulatory decision-making for medical device diagnostic and therapeutic products.

As regulatory science researchers and clinicians who study the use of RWD/RWE and leverage it for research about the safety and effectiveness of medical products, we applaud the agency's effort for its comprehensiveness and thoughtfulness in providing guidance about leveraging real-world data (RWD) to generate real-world evidence (RWE) for medical device products. As FDA advances its efforts in this space, we believe there remain opportunities to take further steps to promote the rigor of RWD-based studies to ensure that subsequent evidence generation can be used appropriately in regulatory decision-making. In many cases, clinical trials (ideally, with more pragmatic than explanatory elements, but which continue to leverage randomization, blinding and control arms to ensure study validity) will continue to be needed. While FDA's draft guidance is specific to medical devices, we believe there is an opportunity to

harmonize common best practices for evidence generation across the agency's ongoing efforts for RWD applications in other regulated medical products (e.g., drugs, biologics).

The FDA's 2017 guidance marked a significant milestone in incorporating RWE into the regulatory framework for medical devices. It provided initial principles and considerations for utilizing RWE in regulatory submissions, acknowledging the potential of RWE to complement traditional clinical trial data, and expedite regulatory decision-making processes. Since the publication of the 2017 guidance, there have been advancements in the understanding and utilization of RWE in regulatory decision-making. The current draft guidance reflects some of these advancements and highlights key differences between the two versions, including enhanced methodological guidance and integration with RWD standards. However, gaps remain in the updated guidance. Specifically, as we discuss below, the FDA could provide more detailed recommendations on study design, data analysis, and validation methods to address concerns about bias, confounding, and data quality. The FDA could also address gaps in the evolving standards for RWD collection, interoperability, and integration, to facilitate consistency and comparability across studies. Moreover, the FDA could address gaps in the updated guidance relating to regulatory pathways for incorporating RWE into premarket submissions, postmaket surveillance, and compliance activities.

Contextualizing FDA's Proposed Guidance to Parallel FDA RWE Efforts for Drugs and Biologics

Moreover, we believe there are provisions in FDA's 2023 RWE guidance for drugs and biologics (entitled, "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") that should be included in this new 2024 guidance for RWE in medical devices.

1. Scope and specificity: The FDA guidance for RWD/RWE to support regulatory decision-making for drugs and biological products provides detailed considerations for the use of RWD and RWE across various stages of drug development and regulatory decision-making. However, the guidance for medical devices lacks the same level of specificity and comprehensiveness. There is a need for more detailed guidance tailored specifically to the unique characteristics and multiple regulatory pathways of medical devices. Although examples are provided in Appendix B, it would be helpful to have additional specific guidance (with further examples) for Class I, II, and III medical devices and based on different types of medical devices – such as diagnostic devices and software-based devices.
2. Data quality and standardization: Ensuing the quality and consistency of RWD is crucial for generating reliable RWE. The drug and biological products RWD/RWE guidance discusses data quality considerations, such as study monitoring, and there is a need for more emphasis on data standardization and interoperability in the context of medical devices. Standardized data capture methods (ideally leveraging unique device identifiers, as we discuss below) and interoperable systems are essential for effectively leveraging RWE in the evaluation of medical devices.
3. Postmarket surveillance and safety monitoring: While the RWD drug and biological products RWD/RWE guidance addresses postapproval study requirements, the medical

device guidance could provide more detailed recommendations for leveraging RWD sources, such as EHR and medical device registries, to support ongoing monitoring and risk management, and emphasize the importance of unique device identifiers to ensure accurate tracking of specific devices.

4. Integration with traditional evidence: Both the drug and biological products RWD/RWE and CDRH's proposed guidance documents acknowledge the importance of integrating RWE with traditional clinical trial data. However, there is a need for clearer guidance on how to appropriately interpret RWE in the context of regulatory decision-making for medical devices because there are many important questions about medical device safety and effectiveness that cannot be answered with RWE. Establishing frameworks for integrating diverse sources of evidence and assessing their relative reliability would enhance the credibility and utility of RWD/RWE in the device regulatory process.

We also offer comments, organized by section and line number, that we think can be used to strengthen this important Draft Guidance.

Background Recommendations

94: FDA highlights the role for RWD in patient experience data, noting that RWD that includes patient experience data may provide new insights into the performance of a device. FDA also signaled its interest in patient experience data for medical devices (specifically implantable) in a new 510(k) guidance issued in September 2023. It could be useful for the FDA to identify connections to the 510(k) reform guidance to show how these different draft guidances are interacting with each other:

- US Food and Drug Administration, Center for Deceives and Radiologic Health. Draft Guidance for Industry: Evidentiary Expectations for 501(k) Implant Devices. 2023 Sep 7. FDA Rockville, Maryland. https://www.fda.gov/media/171835/download

112-114: Although FDA notes that analyses of RWD may provide similar or even superior information to that collected and analyzed through a traditional clinical study, it would also be helpful to acknowledge that there remains a significant and important role for traditional clinical studies. Traditional clinical studies will continue to be needed for medical device evaluations because of the challenges in accurately identifying a medical device of interest given the lack of UDI integration into EHRs and claims data, fragmented administrative claims and electronic health record data that typically precludes monitoring of patients for outcomes of interest as they move across health systems and payers , as well as the difficulties in ascertaining the indications and outcomes of interest from RWD as these data elements are currently operationalized within clinical trials. These data sources (e.g., EHRs, administrative claims) are among the data elements that the FDA identifies are part of RWD in lines 212-218 of this draft guidance. This issue of ensuring accurate identification of the medical product of interest, however, does not apply to drugs or biologics because of the integration of national drug codes into RWD sources and, thus, is a uniquely device-specific issue, and hence should be further addressed in this guidance.

- Rathi VK, Ross JS, Redberg RF. Unique Device Identifiers-Missing in Action. *JAMA Intern Med.* 2023;183(10):1049-1050. doi:10.1001/jamainternmed.2023.3561

Regulatory Context in Which Use of RWE May be Appropriate Recommendations

198-199: FDA notes that it recognizes that RWE can be generated from a variety of RWD sources that are primarily intended for another purpose. However, it's critical that the FDA make clear in the guidance that RWD is characterized by the setting in which it is collected and neither precludes randomization nor pragmatic trials, as defined by the agency in 2016.

- Sherman, R.E., Anderson, S.A., et at. Real-World Evidence – What Is It and What Can It Tell Us? *N Engl J Med* 2016; 375:2293-2297. DOI: 10.1056/NEJMsb1609216

247: FDA notes RWD may be potentially used in a regulatory submission for the generation of evidence to support a petition for reclassification of a medical device under section 513(e) or (f)(3) of the FD&C Act. As our previous research has shown, reclassification decisions for devices in the 515 Program Initiative largely relied on RWE. If RWE is likely to become the primary evidence base for reclassification, then FDA should revise its guidance to prospectively define expectations for the quality and rigor of RWD and RWE used to inform reclassification decisions, especially downclassification or split-reclassification that includes a downclassification.

- Mooghali M, Rathi VK, Kadakia KT, Ross JS, Dhruva SS. Medical device risk (re)classification: lessons from the FDA's 515 Program Initiative. *BMJ Surg Interv Health Technol*. 2023 Sep 28;5(1): e000186. doi:10. 1136/bmjsit-2023-000186. PMID:38033980; PMCID: PMC10687393.

294-301: FDA notes that if a sponsor or institutional review board (IRB) is unclear regarding the applicability of the IDE regulations to a particular RWD collection activity or use, the sponsor or IRB should contact the FDA directly. We suggest additional clarification in this regard to qualify the circumstances under which there may be ethics and informed consent issues for IRBs when considering RWD applications.

303: FDA notes that application of RWD from devices authorized for emergency use authorizations (EUAs) under section 564 of the FD&C Act are relevant to this draft guidance. Given that this section in the guidance concerns RWD for EUAs, such as during the COVID-19 pandemic, it would be very helpful for FDA to publish any insights relevant to medical devices from its COVID Evidence Accelerator to inform RWD efforts in future public health emergencies.

- Chakravarty, A., Roe, L., Lasky, T., et al. Generating Actionable Insights from Real World Data – The COVID-19 Evidence Accelerator. US Food and Drug Administration, Office of the Commissioner. 2021 May 26. https://www.fda.gov/science-research/fda-science-forum/generating-actionable-insights-real-world-data-covid-19-evidence-accelerator

Assessing Data Relevance and Reliability Recommendations

358-359: FDA notes in the draft guidance document that sponsors should consider data related to various demographic characteristics, such as age, sex, race, ethnicity, and other potentially

relevant covariates, and whether the data are representative of the intended use population. We agree that this is an incredibly important factor, and data must be comprehensively collected in order to promote and advance health equity. We also suggest that FDA ask sponsors to consider how various demographics characteristics have been ascertained, particularly for administrative claims and electronic health record data, as these often are not based on patient self-report and could be inaccurate.

- Kadakia KT, Rathi VK, Ramachandran R, et al. Challenges and Solutions to Advancing Health Equity with Medical Devices. *Nat Biotechnol* 2023;41:607-609.
- Nead KT, Hinkston CL, Wehner MR. Cautions When Using Race and Ethnicity in Administrative Claims Data Sets. *JAMA Health Forum.* 2022;3(7):e221812. doi:10.1001/jamahealthforum.2022.1812

364: FDA notes that study protocol and analysis plans should be created prior to analyzing RWD. We agree that the protocol and analysis plan should be created prior to analyzing RWD. In addition, we recommend that all RWE studies be registered prior to when the studies are conducted, with uniform results reporting expectations to ensure their public availability. These recommendations are aligned with recent guidance developed by a public-private consortium for the structured planning and reporting on the implementation of RWE studies of the safety and effectiveness of treatments. Additionally, we recommend FDA establish similar enforcement mechanisms for registering and reporting RWE studies that are consistent with those that FDA has developed and exercised for the registration of traditional clinical trials.

- Dhruva SS, Shah ND, Ross JS. Mandatory Registration and Results Reporting of Real-World Evidence Studies of FDA-Regulated Medical Products. *Mayo Clin Proc*. 2020 Dec;95(12):2609-2611. doi: 10.1016/j.mayocp.2020.04.013. Epub 2020 Oct 21. PMID: 33289654.
- Wang, S. V., Pinheiro, S., et al. STaRT-RWE: structured template for planning and reporting on the implementation of real-world evidence studies. *BMJ* 2021;372:m4856.

Data Availability Recommendations

389-390: FDA notes that use of the device (DI) portion of the UDI, or other structured data and clinical notes, and other exposure in the study population is appropriate. We recommend this as an opportunity for the FDA to highlight the need for interagency work on UDI. Given that the UDI and UDI-DI are rarely available in EHRs and not available in claims data, we recommend FDA provides more specific guidance that investigators must be certain about the use of a specific medical device in clinical care; this will often require manual chart review, as even efforts to leverage natural language processing tools may still carry risks of misclassification of patient and device information:

- Dhruva SS, Ridgeway JL, Ross JS, Drozda JP Jr, Wilson NA. Exploring unique device identifier implementation and use for real-world evidence: a mixed-methods study with NESTcc health system network collaborators. *BMJ Surg Interv Health Technol*. 2023;5(1):e000167. Published 2023 Jan 23. doi:10.1136/bmjsit-2022-000167

- Wang X, Ayakulangara Panickan V, Cai T, et al. Endovascular Aneurysm Repair Devices as a Use Case for Postmarketing Surveillance of Medical Devices. *JAMA Intern Med.* 2023;183(10):1090–1097. doi:10.1001/jamainternmed.2023.3562

408-412: FDA notes as an example that tertiary care hospitalization data may not have adequate data availability to study outcomes that are likely to be diagnosed in an emergency for all patients. In addition to longitudinally for assessing outcomes, there may be insufficient information for adequate risk adjustment if a patient receives a given medical device only at a tertiary care center. Thus, we recommend that RWD sources are required to ensure there is enough information about patient demographics, past medical history, and clinical measures of disease severity to ensure adequate risk-adjustment.

- Dhruva SS, Jiang G, Doshi AA, Friedman DJ, Brandt E, Chen J, Akar JG, Ross JS, Ervin KR, Farr K, Shah ND, Coplan P, Noseworthy PA, Zhang S, Forsyth T, Schulz WL, Yu Y, Drozda JP. The Feasibility of Using Real-World Data in the Evaluation of Cardiac Ablation Catheters: A Test-Case of the National Evaluation System for health Technology Coordinating Center. *BMJ Surg Interv Health Technologies*. 2021;3:e000089.

Relevance and Reliability Recommendations

442: FDA notes the importance of timeliness in relation to RWD, noting the time between data collection and release for research should be reasonable and the RWD considered for the study should reflect the current clinical environment. We suggest highlighting Safety Communications and Recall Events as specific considerations to harmonize with the FDA's draft guidance on the 510(k) reforms, which will consider data on predicate safety.

- US Food and Drug Administration, Center for Devices and Radiological Health. Draft Guidance for Industry: Best Practices for Selecting a Predicate Device to Support a Premarket Notification [510(k)] Submission. 2023 Sep 7. FDA Rockville, Maryland. https://www.fda.gov/media/171838/download

Data Quality and Integrity Recommendations

563-567: FDA notes that if the sample size could be expected to increase in the foreseeable future that sponsors should consider conducting an interim analysis with extant data. As noted above in the comment to line 364, if "interim" analyses are planned, then these should be pre-specified in the study registration and publicly reported.

RWD Methods for Study Designs Recommendations

668-671: FDA notes that a specific type of study design for clinical studies is not endorsed, and that in choosing the appropriate design for studies, using RWD is dependent on the study question, device, outcome, key covariates, and the specific study objectives or hypothesis. While FDA may not endorse a specific study design type, randomized designs with active controls should be the goal as often as possible to provide the most robust evidence supporting reasonable assurance of safety and effectiveness. Randomized clinical trials may not be the

most common evaluation method for medical devices, yet it is important for the FDA to address and emphasize higher quality non-randomized studies. To ensure that these meet the least burdensome requirements, these can be conducted with as many pragmatic elements as possible.

- Sherman, R.E., Anderson, S.A., et at. Real-World Evidence – What Is It and What Can It Tell Us? *N Engl J Med* 2016; 375:2293-2297. DOI: 10.1056/NEJMsb1609216
- Faris, O., Shuren, J. An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials. *N Engl J Med* 2017; 376:1350-1357. DOI: 10.1056/NEJMra1512592.

677: FDA notes that objective performance criteria (OPC) or performance goals are included in study designs. FDA should distinguish between OPC and performance goals, given that the latter is a weaker strength of evidence.

678-679: FDA notes that non-interventional studies, such as comparative cohort studies case-control studies, self-controlled studies, and descriptive studies are possible study designs for generating RWE. FDA should acknowledge there can be significant bias from self-controlled studies in particular, and all observational studies. Although these studies are expected to be conducted, FDA should express its preference for what is stated in line 680: "Randomized controlled trials using RWD to supplement one or more study arms." Further, if observational studies – such as self-controlled studies - are submitted, then they should not include subjective endpoints because these can oftentimes be biased because of patient and/or clinician awareness of treatment allocation.

Clinical Study Using RWD Time Frame Recommendations

739: FDA notes that the time frame for a RWD study is to be defined at the earliest date that the first data element could be collected and extend through the latest date that the last data element could be collected. In Figure 2, it may also be helpful to acknowledge that there may be differences in the standard of care across different RWD datasets in follow-up after index medical device use. For example, follow-up visits may not always occur if there has been a successful procedure (whereas in a traditional clinical trial, there generally is a pre-determined plan for patient follow-up). This challenge points to the importance of using patient-centered mechanisms of data sharing to ensure more comprehensive capture of endpoints.

Conceptual and Operational Definitions Recommendations

781: FDA notes that operational definitions in a study using RWD frequently include combining structured codes or unstructured notes. FDA should note the importance of considering the accuracy of structured codes, because administrative codes often do not provide sufficient granularity and may need to be paired with clinical note review. We recommend FDA require that when study populations or endpoints are based on administrative codes, there is a validation effort to ensure their accuracy.

- Dhruva SS, Jiang G, Doshi AA, Friedman DJ, Brandt E, Chen J, Akar JG, Ross JS, Ervin KR, Farr K, Shah ND, Coplan P, Noseworthy PA, Zhang S, Forsyth T, Schulz WL, Yu Y, Drozda JP.

The Feasibility of Using Real-World Data in the Evaluation of Cardiac Ablation Catheters: A Test-Case of the National Evaluation System for health Technology Coordinating Center. *BMJ Surg Interv Health Technologies*. 2021;3:e000089.

812-820: FDA notes that it may be appropriate to conduct a validation study in which quantitative measurements of the operational definition are compared to a "ground truth" reference standard. FDA should provide further guidance as to when a validation study is warranted. Additionally, if manufactures demonstrate validity in rigorous validation studies, these validated references should be recognized for future evaluations. Furthermore, FDA notes the importance of comparing operational definitions in the RWD to the "ground truth" in the reference standard and cites the example in validating that an administrative billing diagnosis accurately represents a point-of-care diagnosis by comparing an operational definition in administrative claims against an EHR. It would be helpful if FDA could explain in greater detail how a given diagnosis should be rigorously validated using EHR data. We additionally recommend using the example from line 770 of acute myocardial infarction (AMI) to validate this concept.

Protocol Recommendations

931-932: FDA notes that sponsors submit protocol as part of the regulatory submission to FDA for traditional clinical studies. Regarding studies designed to test a hypothesis, FDA recommends that sponsors finalize the protocol and analysis plan prior to reviewing the outcome data and before performing the prespecified analysis. FDA should change from "recommend" to "require."

Elements for Documentation and FDA Review Recommendations

Table 1: FDA notes recommended RWD relevance elements for submission of RWE. It seems particularly important for sponsors to provide FDA with information about how they corrected for redundant data, resolved inconsistencies, and assessed potential for missing data because all of these are particularly important considerations to understanding the rigor of a study conducted using RWD.

Where RWE is Used Recommendations

1064: FDA notes an example of Section 522 submissions regarding RWD. We suggest additional discussion here about the different use cases of 522 studies. FDA could refer to published research that shows how Section 522 studies to date have been used for only one labeling change, suggesting the data being generated may not be of high quality or conducted in a timely manner, and the agency could offer suggestions about how to ensure that rigorous RWD can be used to fulfill Section 522 study requirements:

- Iwaishi, C., Iwasaki, K. A Comprehensive Analysis of Postmarket Surveillance Study Orders: Device Characteristics, Study Statuses, Outcomes, and Potential Contributions. *Ther Innov Regul Sci* **54**, 953-963 (2020). https://doi.org/10.1007/s43441-020-00113-7.

1078-9: FDA notes that besides the safety and effectiveness endpoints, the study also included a secondary endpoint of patient-reported satisfaction with and trust in the software-only device. Although blinding is not always possible, ascertaining patient satisfaction and trust in the software-only device could be affected given that the device was being used by patients (e.g., in the absence of a placebo control).

Lastly, we recommend collaboration with CMS for their guidance on RWD as part of the Transitional Coverage for Emerging Technologies (TCET) pathway, specifically aimed at enhancing innovation while establishing patient safeguards. This initiative aligns closely with the FDA's draft guidance for RWD/RWE to support regulatory decision-making for medical devices, reflecting a pivotal moment where collaboration can shape the landscape of patient care. Considering CMS's recent guidance on RWD and the FDA's draft guidance on RWE, collaborative efforts can facilitate the development of standardized methodologies and best practices, fostering consistency across regulatory evaluations.

- Farmer SA, Fleisher LA, Blum JD. The Transitional Coverage for Emerging Technologies Pathway – Enhancing Innovation While Establishing Patient Safeguards. *JAMA Health Forum*. 2023;4(8):e232780. doi:10.1001/jamahealthforum.2023.2780

In conclusion, we appreciate the chance to comment directly on this FDA draft guidance focused on RWE for regulatory decision-making for medical devices, providing insight from our perspectives as clinicians, researchers, and academics. The new recommendations from the FDA carry the potential to clarify expectations for RWD while advancing the uses of RWD for patients and clinicians to rely on as well as the FDA to further assess RWE for medical device regulation. As the FDA finalizes this draft, we hope the agency will take into consideration the potential ramifications on regulatory standards and transparency of how the FDA employs possible requirements to address regulatory decision-making.

Sincerely,

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