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February 20, 2024

Docket Number: FDA-2023-D-4395

Dear FDA:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your consultation entitled “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices,” which will supersede the prior 2017 guidance on this topic.

ISPOR is a scientific and educational society with many of its members engaged in evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally, across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government, and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

The response to this consultation was led by the Policy Outlook Committee of our most senior advisory body, the Health Science Policy Council. We solicited comments from the ISPOR Institutional Council, Real-World Evidence (RWE) Steering Committee, and several ISPOR Special Interest Groups. The attached document provides a summary based on their comments. We hope they prove useful.

ISPOR would be happy to answer any questions about our response, to serve as a partner, or to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Robert Abbott  
CEO & Executive Director  
ISPOR

## **Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (Docket Number: FDA-2023-D-4395)**

### General Comments with Consideration of Introduction, Background, and Scope (Sections I-III)

We appreciate the FDA's efforts on this guidance which clarifies the Agency's expectations on the use RWE to support regulatory submissions for medical devices. We note the flexibility and broad perspective provided in the guidance to support high scientific standards.

General comments are provided below, followed by comments on specific sections of the guidance document.

- 1) Though the guidance frequently references other related FDA guidance documents, there is no mention or reference of established RWE guidelines, best practices and publications developed outside of FDA, for example, by our organization ISPOR-The Professional Society for Health Economics and Outcomes Research, as well as the International Society for Pharmacoepidemiology (ISPE), the Society of Medical Decision Making (SMDM), the Medical Device Innovation Consortium's (MDIC) National Evaluation System for Health Technology Coordinating Center (NESTcc), or the Duke Margolis Center for Health Policy. We encourage FDA to refer to these publications where applicable throughout the document; they would be most helpful where data quality, fit for purpose assessments, protocol development, study design considerations, and reporting are covered. A short list of relevant references includes:
  - a) HARmonized Protocol Template to Enhance Reproducibility (HARPER) of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force. *Value in Health*. 2022 Oct 1;25(10):1663-72. Additional details are available at <https://www.ispor.org/heor-resources/good-practices/article/harmonized-protocol-template-to-enhance-reproducibility-of-hypothesis-evaluating-real-world-evidence-studies-on-treatment-effects>
  - b) Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value in Health*. 2017;20(8):1003-1008. Available at: <https://www.ispor.org/heor-resources/good-practices/article/good-practices-for-real-world-data-studies-of-treatment-and-or-comparative-effectiveness-recommendations-from-the-joint-ispor-ispe-special-task-force-on-real-world-evidence-in-health-care-decision-making>

- c) NESTcc Data quality and methods framework available at <https://mdic.org/wp-content/uploads/2020/02/NESTcc-Data-Quality-Framework.pdf>
  - d) SPIFD framework to identify fit-for-purpose data: Gatto NM, Campbell UB, Rubinstein E, Jaksa A, Mattox P, Mo J, Reynolds RF. The structured process to identify fit-for-purpose data: a data feasibility assessment framework. *Clinical Pharmacology & Therapeutics*. 2022 Jan;111(1):122-34.
  - e) Other resources pertaining to RWE methods and transparency are available at ISPOR's website under our Real World Evidence initiative:  
<https://www.ispor.org/strategic-initiatives/real-world-evidence>
- 2) Patient Experience Data are stated as a form of real-world data (footnoted in Section II: Background with “patient-generated data” mentioned as a considered RWD source in Section IV), but use of patient reported outcomes (PROs) specifically for regulatory-grade evidence can be challenging. Thus, it would be beneficial to highlight the uniqueness of PROs throughout the document in terms of their validity, collection and analysis.
- 3) Additional detail on how to navigate Investigational Device Exemption requirements in the context of RWD, including the identification of scenarios and exemptions, would be helpful to researchers and developers.
- 4) The guidance does not address the use of non-clinical data, adverse event reports, or secondary use of clinical study data. All of these may be important data sources that elucidate the safety and effectiveness of devices. We suggest that these be addressed in the guidance and/or noted as an area of need for future guidance.
- 5) It would be helpful if the guidance differentiated between *core* requirements and *additional or supplemental* elements.
- 6) Given that RWE harmonization efforts are underway, consideration should be given to real world data obtained from other regions of the world, for example, the DARWIN EU initiative in Europe.
- 7) Though generalizability of the data is discussed in that the RWD sources should be generalizable to the target population with the condition of interest, the guidance does not specify that RWD which includes individuals who are underrepresented in clinical trials is desirable. In other words, the diversity of individuals included in RWD should be considered as an important potential benefit of its use to inform regulatory decisions.
- 8) We encourage FDA to continue sharing RWE use cases for medical devices. In particular, data quality and fit-for-purpose assessments are critical to furthering the use of real-world data for regulatory purposes while reducing duplication of work.

## Regulatory Context in Which Use of RWE May be Appropriate (Section IV)

- 1) Lines 215-216 seem to limit “patient-generated data” as that created, reported, or gathered by patients in home settings. The mention of “home settings” is overly narrow as these data are often collected outside of the home. Perhaps this language can be re-framed such that patient-generated data is that from outside the health system.

## Assessing Data Relevance and Reliability (Section V)

- 1) It would be beneficial to sponsors if the Agency further clarified how data sources and measures may be weighed when making a regulatory decision.
- 2) For line 339-340, sentence could be clarified to: “Whether data are sufficiently relevant and reliable for use will, in part, depend on the particular regulatory decision *to be made*.”
- 3) For line 392, we suggest including more information on core outcome sets when defining clinical outcomes assessments (COAs). Examples of core outcome sets are found at:
  - a) The Comet Initiative: <https://www.comet-initiative.org/>
  - b) International Consortium for Health Outcomes Measurement: <https://www.ichom.org/>
- 4) For lines 414-415, use of supplemental data sources is addressed as being relevant when the RWD source is insufficient on its own. If there are specific questions that are amenable to these supplemental sources, those should be elaborated. The language here also begs the question as to whether the sponsor should not proceed with the RWD source if it is insufficient to answer the scientific questions at hand.
- 5) For lines 466-477, we suggest adding validating patient-reported outcome (PRO) instruments as one of the possible data sources. PRO-specific data collection considerations (for example, related to the timing of data collection, instrument selection, mode of data collection, and patient burden) would also be beneficial in lines 479-512.

## Considerations for Methodologies for Collection and Analysis of RWD to Generate RWE (Section VI)

- 1) Offering some certainty on reliability of commonly used data for acceptable uses would help here. providing commentary on FDA's current thinking on the reliability of commonly used administrative claims databases (for example, CMS' SAF, MarketScan). These data sources have common and known methodologies and would be good if the FDA could give a sense of their thinking on these specific databases' design elements as well as use cases and limitations. FDA has an

opportunity to provide thought leadership to improve upon these databases and encourage the development of universal best practices among databases.

- 2) We suggest that FDA address acceptability of adaptive designs and the incorporation of patient-reported outcomes into RWE studies.

#### Documentation for FDA Review (Section VII)

- 1) A submission completeness checklist would be helpful.
- 2) For line 1000, the ClinicalTrials.gov NCT number is stated as a component of the regulatory submission. Given that ClinicalTrials.gov is not well suited for RWE studies, we suggest that FDA expand this to include RWE-specific registries such as:
  - a) ISPOR's Real World Evidence Registry, available at  
<https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-registry>
  - b) The European Heads of Medicines Agency / European Medicines Agency (HMA/EMA)'s newly released Catalogue for RWD Studies, which expands and replaces the EU PAS Register®). The Catalogue is open to participation from those outside of the EU and is available at  
<https://catalogues.ema.europa.eu/>

#### Appendices

ISPOR finds these appendices useful but asks for clarification in Appendix A about how electronic health records from a multi-site study may be used in regulatory decision making.

**We acknowledge ISPOR members Vignesh Iyer, Kejsi Begaj, and Wai Chee Kuan for their assistance in assembling these comments, as well as ISPOR staff Laura Pizzi and Kelly Lenahan.**