



The professional society for health
economics and outcomes research

Improving healthcare decisions

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December 15, 2023

Docket Number: FDA-2023-D-2318

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 “Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence.”

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 our general membership for comments. 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

Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence.

The ISPOR membership commends the US FDA for undertaking the crucial task of developing draft guidance on the types of evidence that meet the substantial evidence standard to support an adequate and well-controlled clinical study. The release of this guidance reflects progress as science evolves and the willingness to consider innovative research methods increases.

- **Encourage Transparency in Reporting and Disclosing Confirmatory Real-World Evidence (RWE):** ISPOR members recommend that the FDA foster a culture of transparency and encourage sponsors to report and disclose confirmatory evidence based on real-world data/evidence (Section F). In 2018, we joined forces with the International Society for Pharmacoepidemiology (ISPE), the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council (NPC) to form the RWE Transparency Initiative, whose objective is to establish a culture of transparency for study analysis and reporting of hypothesis evaluating real-world evidence studies on treatment effects [1].
- **Provide Further Details on Criteria and Methods for Selecting and Validating Evidence as Confirmatory:** To enhance clarity and consistency in the application of the guidance, we suggest additional details on the criteria and methods for selecting and validating confirmatory evidence. Clear guidelines in this regard will not only assist sponsors in meeting the outlined standards but will also drive clarity in early engagement.
- **Include References to Related Guidance:** ISPOR members suggest citation of relevant existing guidance for cross-reference:
 - Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products [FDA-2022-D-2983] is relevant to Section E (Natural History Evidence) and Section F (Real World Data/Evidence).
 - Another reference relevant to Section E (Natural History Evidence) and Section F (Real-World Data/Evidence) may be the US FDA guidance series for patient-focused drug development, such as “Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders” and “Patient-Focused Drug Development: Methods to Identify What Is Important to Patients”.

Clear reference to these existing validated materials within the guidance document and their location to facilitate access is expected to further support investigators looking to use confirmatory evidence to support a clinical study.

- **Address the Role of Confirmatory Evidence in Enhancing Diversity in Research:** In support of the FDA's efforts to increase the participation of racial and ethnic minorities in clinical research, ISPOR members recommend that the guidance explicitly acknowledge the role of confirmatory evidence in this context. Emphasizing the importance of diverse study populations and encouraging sponsors to include underrepresented groups in confirmatory trials will contribute to the generalizability of study findings.
 - **Offer Partnership on Real-World Evidence:** ISPOR welcomes the opportunity to collaborate with the FDA in the implementation of the guidance, particularly in areas related to the use of real-world
1. LS Orsini, M Berger, W Crown, G Daniel, H-G Eichler, W Goettsch, J Guerino, P Jonsson, NM Lederer, B Monz, D Mullins, S Schneeweiss, D VanBrunt, SV Wang, RJ Willke. Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Roadmap from the Real-World Evidence Transparency Initiative. *Value in Health* 2020; 23(9):1128-36 and *Pharmacoepidemiology and Drug Safety* 2020.

evidence (RWE). We actively collaborate with other organizations on this topic including the International Society for Pharmacoepidemiology (ISPE), the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council (NPC). Our joint ISPE/ISPOR task force has developed 'HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force' [2], and we believe that aligning our efforts will foster advancements in the appropriate use of RWE, ultimately benefitting patients, clinicians, and regulators.

We would like to acknowledge ISPOR members Brittany Carson and Nivantha Naidoo for their assistance in assembling these comments, as well as ISPOR staff Laura Pizzi, Mitch Higashi, Erin Zagadailov, and Kelly Lenahan.