

**2022–2023
Board of Directors**

May 2, 2023

PresidentJan Elias Hansen, PhD
Genentech
San Francisco, CA,
USA

Docket Number FDA-2022-D-2983

President-ElectBrian O'Rourke, PharmD
Brian O'Rourke
Healthcare Consulting
Ottawa, ON, Canada

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 “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products.”

Past PresidentIsao Kamae, DrPH, MD
University of Tokyo
Tokyo, Japan

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.

DirectorsEberechukwu
Onukwugha, PhD
University of Maryland
Baltimore, MD, USALotte Steuten, MPhil, PhD
Office of Health Economics
London, England, UKDavid Thompson, PhD
Open Health Evidence &
Access
Boston, MA, USABeth Devine, PhD
University of Washington
Seattle, WA, USAMarlene Gyldmark, MPhil
Roche Diabetes Care
Basel, SwitzerlandAndrea Manca, MSc, PhD
University of York
York, England, UKDong-Churl Suh, PhD
Chung-Ang University
Seoul, South Korea

The response to this consultation was led by the Policy Outlook Committee of our most senior advisory body, the Health Science Policy Council. To engage our membership, we consulted with interested members of our Real-World Evidence Steering Committee, Institutional Council (ie, industry and consulting), as well as our Real-World Evidence, Rare Disease, Statistical Methods in Health Economics and Outcomes Research (HEOR), Oncology, Precision Medicine and Advanced Therapeutics, and Patient-Centered Special Interest Groups, and solicited our general membership for comments. The attached document provides both summary and line-by-line responses based on their comments. We hope they prove useful.

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

Sincerely,

Robert Abbott
CEO & Executive Director
ISPOR**Treasurer (2020-2023)**Sean D. Sullivan, BSc,
Pharm, MSc, PhD
University of Washington
Seattle, WA, USA**CEO & Executive Director**Rob Abbott
ISPOR
Lawrenceville, NJ, USA

“Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry”

ISPOR General Comments, May 2, 2023

1. This is a very important document and a very welcome step forward from the FDA on this issue. In general, the draft guidance provides clear and thorough discussions of the key considerations involved in rigorous use of external control arms (ECA) for safety and efficacy/effectiveness studies.
2. There are a number of places in the guidance where concerns are cited as being particularly relevant for real-world data (RWD) sources, eg, administration of treatment (l. 197), index dates (l. 225), missing data for comparability (l. 358), blinding of results (l.392), intercurrent events (l.454), misclassification (l. 461). It may be helpful for those considering RWD sources for ECA use to see a consolidated summary or table of these concerns to help focus those considerations.
3. It would be useful to clarify whether this guidance is intended to apply equally across different phases of drug development where ECA's could be useful – mainly II, III, and IV – or whether it is targeted primarily at registration studies meant to establish efficacy. If it is intended for use across phases, are there any different considerations depending on phase?

ISPOR Detailed Comments

Lines 47-90. The section could also indicate that the choice of an external control might be evaluated on a case-by-case basis. The document acknowledges that there are situations when the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low. However, it might be also added that there are circumstances where an external control could be considered in place of an internal control where the latter would not be ethical or feasible at all.

Lines 57-60. According to reference 11 [21 CFR 314.126(b)(2)(v)] historical control arms are usually reserved for special circumstances. According to reference 12 [Section 505(d) of the FDCA] substantial evidence is defined as evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved. Neither reference gives the impression that historical control arms form adequate or well-controlled studies or provide substantial evidence. Should this sentence be something like the following? “However, it is not clear as to how close these other types of control are to providing substantial evidence in the same way as that from adequate and well-controlled clinical investigations as defined under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Lines 103-112. We agree with the draft guidance that the selection of the external control arm and the analytical approach should be documented during the study protocol development phase rather than later when the single-arm trial is already completed. We also agree with Food and Drug Administration's (FDA) note that sponsors should document and describe in the protocol all data sources accessed during the design of the control arm. However, we suggest expanding on this guidance by emphasizing the need for the identification and selection of data sources to be conducted in an unbiased way, for example, informed by a systematic collection of related evidence and a feasibility assessment of available real-world databases with the contribution of clinical experts. We also propose that the FDA consider encouraging sponsors to document this selection process as part of the feasibility exercise in a structured way to allow reproducibility

of findings; this can be achieved by following well-established templates and checklists to record key parameters and quality elements from each data source.^{1,2} Unbiased selection of the most comparable control arm, either from clinical trials or RWD sources, will not only increase transparency and confidence in the comparative treatment-effect estimates but also will provide a clear justification in situations when two or more data sources may fall short of mirroring the selection criteria of the single-arm trial. In these situations, when external control sources are impartially identified, the guidance should highlight that a robust rationale (based on proposed considerations for assessing comparability of data in this draft guidance) is needed to justify the selection of data sources to support the base-case and potential scenario analyses. This exercise can further inform situations in which findings from different data sources bring inconsistent results. Given the FDA's attention to the totality and consistency of the data from different data sources in previous externally controlled trial submissions, unbiased selection of all relevant sources would be key. This will hopefully help to guide sponsors in future FDA single-arm submissions in the same disease area by either re-using previously verified data sources or supplementing with additional datasets as needed.

To parallel this valuable guidance, the FDA could provide a publicly-accessible and updated catalogue of instances in which real-world evidence has been included in labeling, along with any considerations on the context of use, such as type of decision (accelerated approval, full approval, label extension), data source (eg, CIBMTR) or study designs (eg, external controls, placebo augmentation)? This could be provided in the same spirit as the very helpful table on surrogate outcomes linked below.

- o <https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure>

Lines 203-211. We agree that the factors mentioned in this paragraph can vary, sometimes significantly, between randomized controlled trials (RCT) and RWD populations, and can affect both choice of treatment and outcomes. If such factors impact the choice of treatment, other elements of care, adherence to treatment and effectively influence the results of the externally controlled trial, those factors should be taken into account.

Line 250. In case a choice of index date is unclear or not readily identifiable, attempts could be made to identify a surrogate discrete event which might be helpful to identify a suitable index date in the externally controlled trial.

Line 258-267. Given the considerations involved in blinding outcome assessments in RWD, we would suggest further elaboration of the discussion on this topic to better understand the circumstances when 'blinding' might be recommended.

Lines 314-319 (plus 449-456). This section could also mention subsequent therapies or salvage or rescue therapy as a specific intercurrent event. The glossary later mentions rescue therapies as intercurrent events, but they are not specifically noted in the main text. Earlier in the section, the challenges of using subjective endpoints, such as objective response rate (ORR) and progression-free survival (PFS), are noted. However, objective endpoints such as overall survival (OS) are likely to be impacted by subsequent therapies. This can

¹ https://www.ispor.org/docs/default-source/ispor-good-practices-for-outcomes-research-index/ispe_ispor-joint-task-force-report_final.pdf?sfvrsn=aad13fef_0

² <https://www.bmj.com/content/363/bmj.k3532>

be an important source of bias since patients in clinical trials can usually be expected to have better and faster access to rescue therapies (including further investigational agents) than patients in real-world clinical practice. A comparison of clinical trial to RWD OS may therefore become favorable, even when the comparison indicates no or even negative PFS benefit.

Lines 419-429. In addition to the a priori plans for detection of balance, as well as for the "strategy to account for differences in baseline factors and confounding variables between arms" (lines 405-6), a pre-specified plan to remedy balance issues should be included in the statistical analysis plan (SAP). These should specify both the thresholds, and remedies (in a pre-specified order).

Lines 498-500. This section could also explicitly request that sponsors provide a detailed explanation of the factors that they consider make a conventional RCT infeasible, commercially non-viable or unlikely to generate relevant evidence within an acceptable time frame.

Lines 509-511. Regarding provision of patient-level data, we would propose that further guidance be provided on format of documentation for submission to FDA, guidance on how data should be managed in order to meet anonymization requirements (where appropriate), and the process data owners follow to submit data to FDA.

ISPOR would like to acknowledge Grammati Sarri, James Signorovitch, and Kumar Mukherjee for their assistance in assembling these comments.