

**2018–2019
Board of Directors**

February 4, 2019

PresidentFederico Augustovski, MD, MSc, PhD
Institute for Clinical Effectiveness
and Health Policy
Buenos Aires, ArgentinaDr. Scott Gottlieb
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002**President-Elect**Nancy J. Devlin, PhD
Office of Health Economics
London, England, UK

Dear Dr. Gottlieb:

Past PresidentShelby D. Reed, RPh, PhD
Duke University
Durham, NC, USA

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to the U.S. Department of Health and Human Services Food and Drug Administration's call for comments on the "Framework for the FDA's Real-World Evidence Program" (Docket No. FDA-2018-N-4000). We strongly agree that these are important issues to address with input from a wide variety of stakeholders and thank the Department for this opportunity to provide our comments.

DirectorsMeindert Boysen, PharmD, MSc
National Institute for
Health and Care Excellence
Manchester, UK

ISPOR is a scientific and educational society with many of its members engaged in some aspect of health economics and outcomes research (HEOR) related to evaluation of pharmaceuticals. Real-world evidence and real-world data are a key area of interest for HEOR professionals. Our membership includes over 20,000 individuals 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 (including some HHS/FDA employees), 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.

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We have chosen to respond to selected sections where the recommendations were particularly relevant to our mission. This response was formulated with the assistance of ISPOR's full membership as well as our most experienced real-world evidence experts.

Rok Hren, PhD, MSc
Point.of.Care and Siemens
Healthineers
Ljubljana, Slovenia

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

Raoh-Fang (Jasmine) Pwu, PhD
Ministry of Health and Welfare
Taipei, Taiwan

Sincerely,

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First, we would like to congratulate the US Food and Drug Administration for producing a comprehensive implementation outline for its real-world evidence (RWE) program. Real world data and RWE are key building blocks to understanding real world usage and effects of pharmaceutical products. ISPOR, as the leading professional society for health economics and outcome research, and our members have a vested interest in working with the FDA on appropriate use of RWE to bring innovations and advances faster and more efficiently to patients who need them. While this framework touches on many aspects related to the usage of RWE, there are several places where the discussion is especially relevant to ISPOR and its members; therefore, our comments are confined to those areas.

Randomized Controlled Trials Integrated into Health Care Systems (page 11)

We welcome the recognition of the importance of both “hybrid design” and “pragmatic” clinical trials in generating evidence of product effectiveness. Whilst the FDA are correct in saying that the integration of clinical trials into health care systems and capturing outcomes from clinical practice is not new, the value of this approach has increased due to both (i) greater awareness of the importance of understanding the impact of treatment on patients in routine clinical practice, and (ii) recognition that this offers the potential to reduce the costs of conducting trials, which is increasingly becoming a barrier to their use.

Observational Studies Using RWD to Generate RWE: Causal Inference (page 11)

In this section, there is discussion about issues that affect the ability to draw reliable causal inference from secondary (retrospective) data analytic studies, including the divergent nature of the literature surrounding comparisons of results from observational studies to randomized controlled trials.

While “traditional” randomized interventional studies (RCT) are the favored approach for demonstrating causality, they also suffer from some limitations such as selection bias and post-randomization confounding due to differential adherence, loss to follow-up, concomitant therapies, and other consequences of allowing usual care. Observational studies better reflect patient outcomes in the treated patient population, across a variety of healthcare settings, and can be conducted in a more cost-effective and efficient way than traditional randomized clinical trials, as well as providing a basis for inference of causality if designed and conducted properly.

Many standards, guidelines, and tools have been developed for the design, conduct, and reporting of observational studies, including the FDA’s own Pharmacoepidemiologic Guidance

(for safety studies) and the ISPOR Good Practices for Outcomes Research Reports. Many of the recommended practices are equally applicable in the regulatory context because they focus on important methodological issues that are of concern to FDA – e.g. study design to minimize biases (selection, information, confounding), data quality, data linkage, handling missing data, analysis methods to minimize bias (matching, restriction, multivariate modelling, sensitivity analysis), choice of database, validation of endpoints – as well as transparency in reporting.

Observational studies structured accordingly can be potentially valid sources of RWE for regulatory decision-making. While efforts such as the ‘RCT DUPLICATE’ and ‘OPERAND’ projects to replicate RCT results “using more rigorously designed observational studies” as a means to gain greater confidence in the ability of observational approaches to establish causal inference of effectiveness are important, some level of variation in results can be expected even among the most rigorously designed and conducted observational study and a corresponding RCT. Accordingly, additional insight is needed into the Agency’s thinking on what is an “acceptable” level of variation as well as what the additional quantity of such efforts the Agency would like to see and who should conduct these analyses.

We also would encourage the Agency to look at the totality of evidence: RCT, Observational, and any quasi-experimental studies in a continuum. Observational studies may look at slightly different patient populations than RCTs and, in cases when their results differ, there may be very valid reasons for this disparity, for example - results can be explained in a reasonable clinical and/or statistical framework. Also, if the differences between the patient populations analyzed are relatively small then there is more reason to take the results as part of the continuum of truth about a treatment effect rather than discount such results as spurious, particularly if the study has been done in a dataset that trusted as source data in that particular disease area.

Data Standards, Reliability and Relevance (page 14)

We appreciate and very much agree with the Agency regarding selecting data based on suitability to address the specific regulatory question and agree that the Pharmacoepidemiologic Guidance is a very relevant place to start. However, we would also caution keeping the perspectives very much focused on the observational research setting and not straying back to the RCT mindset when evaluating data sources. Criteria that are too stringent, for example - expectation of same or similar variables from the RCT data sets in observational research, will only lead to frustration on both the parts of the Agency and data submitter.

We are aware of other agencies and data experts who are also looking at minimum data set models for RWE data evaluation: (i) South Korea (HIRA's guidance for understanding the relevant methodologies for collection and analysis of RWD in terms of HTA), (ii) Europe (EUnetHTA WP5) and the European Medicines Agency (EMA) activities regarding minimal datasets and qualification procedures for disease specific registries, and (iii) Observational Health Data Sciences and Informatics (OHDSI) consortium on the Observational Medical Outcomes Partnership (OMOP) common data model. These are a few efforts in which our members are actively participating. We encourage the Agency to continue to engage with other experts and agencies, especially those outside the United States, who are also looking at data models and other methods to evaluate reliability and relevance of registry and electronic health care data. Creating globally relevant standards reduces duplicative efforts and encourages producers of these data to adhere to standards.

Addressing Data Gaps (page 17)

We agree that the issues enumerated in the framework in this section are important, however the distinct issue of item-level missing data (no value present for a variable at a time point when other data for that patient are available) is not discussed. This is highly relevant issue for RWD and the resulting RWE and one that ISPOR members are currently working on in our statistical methods special interest group. Issues of 'missingness' could also be informed by experience in the RCT space but would need to be tailored to RWE.

Data linkages are highly relevant as discussed in the framework. Interoperability and integrating data sources are highly desired by almost all outcomes researchers in the United States. As mentioned this would allow the ability to follow a patient throughout their healthcare trajectory from outpatient, inpatient, pharmacy, and diagnostic testing, increasing the richness of the data and allowing removal of duplicate patients from the datasets. One benefit that is not mentioned is the ability to then appropriately pool datasets, thus increasing sample size and statistical power that could also mitigate some of the issues mentioned previously regarding the trust and transparency in RWE studies as compared to RCTs.

Potential for Study Designs Using RWD to Support Effectiveness (page 19)

We agree that study designs for RWD studies can take many forms and were happy to see each discussed here in the framework. However, we would emphasize that the research, clinical, and

regulatory questions an investigator seeks to answer, among other factors such as the disease area, should guide the selection of evidence generation approach – including study design and application of randomization. The forthcoming guidance in these areas should provide the necessary flexibility to operationalize this fundamental principle.

We also agree that transparency and clarity of reporting of RWE studies, including retrospective observational studies, is an important element in building trust in RWE and enabling reproducibility of study results. In particular, starting on page 20 - the discussion of observational study designs is especially relevant; we were encouraged to see mention of the recently published ISPOR/ISPE Special Task Force recommendations on good procedural practices for treatment effectiveness studies. We agree that building on FDA's experience with pharmacoepidemiology studies for safety makes really good sense. Additionally, ISPOR is organizing efforts around ways to increase transparency and trust in secondary (retrospective) data analysis studies, including considerations around registration and reporting requirements that would fit especially well with the program item on page 22 and would invite active FDA involvement in these efforts.