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ISPOR  
Lawrenceville, NJ, USAKaren Facey, PhD  
University of Edinburgh  
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Scotland, United Kingdom

Dear Dr. Facey,

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership regarding the call for comments on “Real-world evidence to support HTA/payer decisions on highly innovative technologies - Actions for stakeholders.” We strongly agree that these are important issues to address with input from a wide variety of stakeholders and thank you for this opportunity to provide our comments.

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 using health technology assessment. 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, 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 – including our real-world evidence (RWE) transparency initiative.

This response was formulated with the assistance of ISPOR’s most representative scientific membership group – the RWE special interest group and our RWE transparency advisory team. We also polled our full membership for comments. It was reviewed by and approved by our current President – Nancy Devlin and myself.

ISPOR appreciates the opportunity to comment on this guidance on behalf of its members and would be pleased to respond to any questions the you may have. Attached are our comments as requested – we will also file these through the Survey Monkey link provided.

Sincerely yours,

Nancy S. Berg  
CEO & Executive Director  
ISPOR

**State any suggested alterations or additions to the proposed actions in sections 4 and 5 of the paper, by referring to the number of the recommended action.**

1.2 The term "evidence bar" requires further clarification. Is this in reference to the quality of real-world evidence (i.e. low level of missingness) and/or the specific type of real-world evidence to answer a question?

2.4 'Request RWE generation plans from companies with links to protocols or plans for data collection and analysis' – ISPOR and the RWE Transparency Partnership agree that access to study documents, preferably prior to data analysis is a key component to a transparent dialogue around RWE generation which can increase the credibility of the results assuming that the study is of high quality. We might suggest that you clarify what is meant by 'request links to....' – is the recommendation for researchers to post the protocol and plan on a public study registry with a link to these documents? If so, the language should be even more explicit about what is recommended. While current registry sites do exist, they aren't always completely fit for purpose for RWE studies, particularly those performed on secondary data. However, there are still ways to post and upload appropriate documents which can be a 'good enough' solution for such a request.

2.5 This recommendation assumes that HTA bodies / payers have systems, frameworks and processes in place to allow for RWD collection or managed entry agreements. As implied in Section 3, this may not be the case. An important recommendation is to encourage HTA bodies / payers to establish systems and frameworks to allow for early access and ongoing RWD collection to inform access decisions.

4.1 Prior to developing an RWE plan, an assessment should be undertaken to establish those data needs of stakeholders that cannot be collected through the clinical trial program. Ideally this would be discussed and agreed with each stakeholder group in advance of developing the plan. Where data can be collected within the clinical program, all efforts should be undertaken to do so to ensure that RWE studies are employed appropriately where they provide the most relevant data.

4.3 and 4.4 and 8.5: ISPOR and the RWE Transparency Partnership highly supports these recommendations for Industry (and any RWE researcher). Ensuring that analytic plans and protocols for relevant real-world evidence studies, especially hypothesis evaluating treatment effect (HETE) studies or those looking at causal inferences, are available to HTA and payer bodies is key to increasing the transparency of this research. This allows the decision makers the ability to evaluate the quality of the research study and credibility of results. We agree that supporting a study registry like existing clinical trial registries would be a large step forward in building a culture of transparency in real-world research.

The right mix of incentives is needed to encourage the registration and reporting of HETE studies. This could eventually include HTA and payer guidances stating that registration (and, depending on timing, public reporting) are prerequisites to the consideration of HETE studies. However, it would be premature to "insist" on registration and reporting (Recommendation 8.5) of HETE studies until there is an appropriate location to do so efficiently. Study sponsors should not be penalized if existing registration sites are impractical to use for these types of studies.

The definition of major RWE studies is unclear. What criteria would be used to define a major RWE study? Is the focus only on effectiveness studies? Would a comprehensive registry of all RWE studies be feasible?

4.5 Industry should consider how to action multi-company collaboration even beyond disease based registries. For example, collaboration to develop a natural history model for the disease; a case study for this is Project HERCULES in Duchenne muscular dystrophy.

### **Are there any initiatives underway that would support implementation of the recommendations?**

The RWE Transparency Initiative is a collaboration and ongoing effort between ISPOR, the International Society for Pharmacoepidemiology (ISPE), the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council (US). The objective of this initiative is to establish a culture of transparency for study analysis and reporting of hypothesis evaluating real-world evidence studies on treatment effects. <https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative>

Several of the recommendations to industry/researchers and HTA/payers in this report align closely with the recommendations from the transparency initiative. We recommend that you read our draft white paper [https://www.ispor.org/docs/default-source/strategic-initiatives/improving-transparency-in-non-interventional-research-for-hypothesis-testing\\_final.pdf?sfvrsn=77fb4e97\\_6](https://www.ispor.org/docs/default-source/strategic-initiatives/improving-transparency-in-non-interventional-research-for-hypothesis-testing_final.pdf?sfvrsn=77fb4e97_6)

### **Do you know of any mechanisms that could support the development of the proposed multi-stakeholder learning network – recommendation 9.0 on page 10?**

We agree that multi-stakeholder collaboration is critical to advance the generation and appropriate use of relevant and credible RWE to answer HTA and payer questions about highly innovative technologies and that a “multi-stakeholder collaborative learning network” is needed support this goal. Prior to establishing a new network, an evaluation of existing networks should be performed to establish if these have the potential to meet the proposed objectives, either as is or through further development. One example is the GetReal initiative established in 2018 under the auspices of the EU-funded Innovative Medicines Initiative (IMI), but several other networks exist and should be given consideration such as The European Health Data & Evidence Network (EHDEN) and the national programme ETAPES in remote patient monitoring in chronic disease particularly chronic heart failure.

Should a bespoke network that is specifically focused on driving the objectives of the paper forward prove to be desirable, then it should have appropriate membership to be recognized as an authoritative body, both at the multi-country and national level, that can act quickly and effectively to implement the recommendations.