ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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January 28, 2025

Dear CDA-AMC:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your consultation entitled "Consultation of Methods Guide."

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 ISPOR Science and Health Policy Initiatives Team and Health Technology Assessment (HTA) Council. Comments were solicited from the ISPOR general membership, the attendees of the 2024 HTA Roundtables, and from those involved in all of ISPOR's 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

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Consultation on Methods Guide

ISPOR commends Canada's Drug Agency (CDA-AMC) on their draft health technology assessment (HTA) methods guideline. Overall, we feel that the draft is well written and clearly describes the HTA process within CDA-AMC. Our members had several comments that we felt would make the document stronger.

We received several comments requesting clarification on the process for the collection of feedback from patient representatives and the general public, and how this information is used to improve decision making. In addition, more information was requested on the methods for demonstrating that the outcomes chosen for HTA are those that matter most to patients. The inclusion of patients is critical to having a better decision-making process and understanding of the needs of those who require technology. ISPOR also commends CDA-AMC for adding their first patient representative, Maureen Smith, to their Board of Directors and feels this is a positive trend in the HTA community that we hope to see more broadly adopted across HTA bodies worldwide.

Please clarify the use of the word "harms" on page 2, line 5. It was not clear whether you mean adverse events, side effects, or both.

Under the section "Research Question and Scope," several comments were made around the use of the terms efficacy, effectiveness, and real-world setting trial. One may want to consider less dichotomy between effectiveness and efficacy. The book *Causal Inference* by Hernan and Roberts (1) states, "Rather than insisting on an artificial efficacy-effectiveness dichotomy, it may be more helpful to accept that all causal effects are placed somewhere along the effectiveness continuum." In addition, there was confusion around the term on page 17, line 15 entitled, "real-world setting trial". The use of the word trial is not needed in that statement as effectiveness is used when data are collected in non-interventional real-world settings. To further strengthen the use of causal inference and real-world evidence (RWE), it is suggested to add external control arms when referring to single arm trials. Also relating to RWE but in another section, on page 11, line 18, it suggests that randomized controlled trials provide evidence with lower external validity than RWE. This conclusion depends on the specific protocol design, and we suggest using less definitive language.

Under the section, "Target Estimands," it was suggested to mention the increased reliance on assumptions of estimands compared to established treatment estimands (eg, those included in policies or guidelines). There are also 5 attributes in the ICH estimand framework, not 4 as mentioned in the document. Intercurrent events may often be re-classified as attributes regarding the population, treatment, or endpoint, and we recommend that these are accounted for to allow for better harmonization with the PICO framework. The ICH addendum states: "Precise specifications of treatment, population and variable are likely to address many of the intercurrent events considered in sponsor and regulator discussions of the clinical question of interest." The Statisticians in the Pharmaceutical Industry (PSI) HTA Special Interest Group webinar on the use of Estimands and PICOs was recommended for more information. (2)

Under the section, "Critical Appraisal of Pivotal and Other Clinical Interventional Trial Evidence," it is recommended to include the need for an independent Data Monitoring Committee to oversee data collection and endpoints. Methods for evaluating data quality, specifying the need for qualitative evidence to demonstrate content validity, and clarifying whether primary research is required for validity (beyond expert opinion/literature) should also be addressed. The guidelines should also clarify whether face validity is captured under existing categories and include guidance on acceptable time points for interim results

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.

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submission during the HTA process, along with minimum follow-up data requirements. Additionally, it would improve clarity to separate reliability from validity or retitle the section, focusing on meaningful within-patient change thresholds instead of minimally important difference with updated references on meaningful change (current references do not reflect the current thinking in this area). The inclusion of other estimands, such as those evaluated via ROBINS-I (3) or RoB 2 (4), should be considered. Lastly, clarification of phrasing related to causal interpretation and the inclusion of the term "transportability" from causal inference literature are recommended.

Under the section, “Critical Appraisal of ITCs,” clarification is needed in cases where differences in patient characteristics exist on how to determine if any of these differences are likely to be modifiers to the relative treatment effects. It is also recommended to clarify the review process by explaining transparency and accountability measures. This would be enhanced by having a list of recommendations in this section. Under the section, “Qualitative Research,” please clarify the statistical analysis methods CDA-AMC aims to include and explain bias assessment methods. Please also clarify the source of qualitative research, if it comes from the sponsor or is identified or generated by CDA-AMC.

Overall, the CDA-AMC’s draft guidance, *Consultation on Methods Guide*, provides a promising framework for health technology assessment in Canada and we look forward to seeing the final version. We acknowledge ISPOR HTA Council Chair Jessica Daw for her assistance in assembling these comments, as well as ISPOR staff Laura Pizzi and Kelly Lenahan.

(1) Hernán MA and Roberts JM. *Causal Inference.* CRC Press: 2011.
(2) Allignol A, Remiro-Azócar A, Hemmings R, and Latimer N. Estimands, PICOs and Co. - Are we losing or gaining in translation? PSI HTA SIG Webinar. December 7, 2023. Accessed January 13, 2025 from: https://www.psiweb.org/vod/item/psi-hta-sig-webinar-estimands-picos-and-co.---are-we-losing-or-gaining-in-translation.
(3) Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
(4) Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

2 Wang, SV, Pottegård, A, Crown, W, et al. 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. Pharmacoepidemiol Drug Saf. 2023; 32(1): 44-55. doi:10.1002/pds.5507