ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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May 31, 2022

Dear EUnetHTA:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your Methodological Guidelines consultation "**"D.4.3.2 Direct and Indirect Comparisons."** We thank you for the opportunity to comment on these draft guidelines.

ISPOR is a scientific and educational society with many of its members engaged in evaluation of 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 members from our Indirect Treatment Comparisons and Network Meta-Analysis Task Force, with comments solicited from a number of our membership groups including our Health Science Policy Council, Institutional Council, HTA Roundtables, Statistical Methods Special Interest Group, and Systematic Reviews Task Force. The attached document provides a synthesis of their comments. We hope they prove useful.

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 report.

Sincerely,

Nancy S. Berg
CEO & Executive Director
ISPOR

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D4.3.2 – Guideline on comparators and comparison s	ISPOR	General		It is ISPOR's understanding that the primary purpose of the EUnetHTA document is to describe the methods most commonly used for direct and indirect treatment comparisons to provide guidance to assessors in the context of the EU regulation for joint clinical assessment of health technologies.	
D4.3.2 – Guideline on comparators and comparison s	ISPOR	General		ISPOR appreciates that the document is a methodological guideline and not a prescription which indirect comparison methods are accepted by HTA decision-makers. One can think of many modifications to the methods described in the EUnetHTA document that may improve the relevance and credibility of an indirect comparison given the evidence at hand relative to the research question of interest. We have seen a lot of methodological development for indirect comparison studies in the past decade, and this is expected to continue for the foreseeable future, especially when more and more studies used for regulatory approval do not follow the standard randomized controlled trial (RCT) design. With this in mind, we like to emphasize a few general points here below that are important for any indirect comparison study, whatever the analytical method, and we would recommend incorporating this information in the guideline document. In addition, we raise a number of specific points.	
D4.3.2 – Guideline on comparators and comparison	ISPOR	General		The purpose of a meta-analysis (MA), network meta-analysis (NMA), or another anchored indirect comparison method for RCTs is to estimate the relative treatment effects between	

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s				competing interventions to inform decision-making for a specific target population of interest. This means that the study population of each of the individual studies included in the evidence synthesis needs to be representative of the target population of interest, which is the case when there are no differences in effect-modifiers between the study populations and the target population. If this requirement for a *relevant* (N)MA or anchored indirect comparison is met, then there are no differences in patient-related effect modifiers between the different RCTs either, a requirement for a *credible* NMA or anchored indirect comparison. Assessing an (N)MA in the context of the decision problem shows that MA and NMA rely on the same assumptions and illustrates the somewhat irrelevant distinction between the concepts of homogeneity, similarity, and consistency as described in the EUnetHTA document. We may even want to avoid using these terms as these are not used consistently in the evidence synthesis literature anyway. To simplify things: 1) For the findings of an (N)MA to be relevant, there should not be systematic differences in patient-related effect-modifiers between the evidence base and the target population of interest; and 2) for a credible NMA (or anchored indirect comparison) we need a connected network of RCTs without systematic differences in known and unknown effect modifiers (related to patient characteristics, study design characteristics, and contextual factors) between studies.	
D4.3.2 –	ISPOR	General		The scientific literature	

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Guideline on comparators and comparisons				provides relevant papers on NMAs specifically tailored to decision-makers and other consumers of these kinds of studies. One publication that is missing and that we like to highlight is the ISPOR guidance paper on NMA. (Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, Salanti G. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17:157-73). This paper provides a systematic overview of the criteria to assess the relevance and credibility of NMA studies.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	General		Increasingly, we are faced with an evidence base where for one or several of the competing interventions of interest there is no RCT available; only single-arm studies. A related challenge is disconnected networks. Unanchored indirect comparison studies rely on the assumption of no differences in effect-modifiers AND prognostic factors between single arm or disconnected studies, which is stronger than the assumption of no differences in effect-modifiers for anchored indirect comparisons. However, the statement by EUnetHTA that indirect comparisons involving single-arm trials and disconnected networks are highly problematic may lead decision-makers to automatically reject such indirect comparisons. This does not serve decision-making well, as the alternative is making decisions based on between-	

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				trial comparisons in the absence of an explicit analysis. Furthermore, a requirement that an indirect comparison of disconnected networks is only acceptable when it is based on full individual patient data (IPD) from all studies included is not in line with the reality of data availability. More often than not researchers performing indirect comparisons to support an HTA submission have only access to IPD for a subset of studies included. Definitely, more research is needed regarding appropriate indirect comparison methods for these kinds of scenarios. However, at this point in time, ISPOR recommends emphasizing that a bespoke and innovative methodological approach to synthesizing a challenging evidence base can still be informative and acceptable as long as it is transparent, adheres to common evidence synthesis principles (e.g. consistency), and maximizes the use of available IPD and benefit of randomization from the RCTs that are available.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	General		In the context of the discussion about the credibility of an indirect comparison using studies other than only RCTs (e.g. observational evidence) for decision-making, we like to highlight the potential trade-off between internal bias and external bias. Internal bias relates to suboptimal internal validity (i.e., presence of selection bias, information bias, or confounding bias) in the primary studies included in the evidence synthesis. External bias relates to the "mismatch" between the target population of the decision problem and the study	

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Sub-deliverable	Comment from	Page number	Line/ section numbe r	Comment and suggestion for rewording	Editorial comment?
				populations of the primary studies. For example, do we prefer an indirect comparison where for one of the RCTs in the network the study population is different from the target population regarding an important effect-modifier (external bias), or an indirect comparison where we replace this study with a non-randomized comparative study with residual confounding that is in exactly the correct population (internal bias)? Both analyses provide suboptimal results for decision-making and it may be unclear which analysis is preferable. ISPOR recommends that EUnetHTA outlines such a potential trade-off in their guideline document, rather than only stating the concerns with indirect comparison studies involving observational evidence.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	General		Adding illustrative examples to the document will give greater clarity on the factors the assessors will take into consideration to assess the appropriateness of the method(s) and assumptions the manufacturer has used in their indirect comparisons.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	General		Structure of guideline: The document currently acknowledges the presence of different data availability settings, however it is currently structured by the type of analysis. I found this led to confusion as I reviewed, because throughout the document (i.e. Section 5 on population-adjusted comparisons and Section 6 on Non-randomized comparisons) it is unclear if the text refers to connected or disconnected networks and anchored vs unanchored comparisons. To	

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				avoid confusion, the guideline would benefit from being restructured based on the data availability of the research question instead of the type of analysis. With this approach, the guideline would outline different data availability situations and provide the suitable comparison methods per situation for the purposes of the JCA.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	General		Observational evidence can be very useful supplementary information as part of any evidence synthesis, including indirect comparisons. The U.S. Agency for Healthcare Research and Quality is just now finishing up an update of its Methods Guidance for use of Non-Randomized Trials in Systematic Reviews. Perhaps that document would be a helpful cross-reference for EuNetHTA	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	22	Section 5.1 and 5.2	The Bucher method is special case of fixed effects network meta-analysis with only 2 RCTs; no need to present it separately. The method by Lumley is not really used. Consider moving it to an historical appendix.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	4-5	69-146	The summary, perhaps due its brevity, sounds more stringent and less clear in places than the actual text of the guidance. E.g.: "If any of these assumptions is violated, the results of the corresponding evidence synthesis do not provide a meaningful estimate of treatment effectiveness." However, the subsequent sections discuss methodological approaches that help an analysis be informative even when some basic assumptions may not hold completely. Perhaps substitute "may not" for "do	

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				not".	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	6	164-181	The tone of the document switches from being guidance in some sections to quite prescriptive in others. We suggest the tone should be reviewed throughout to reflect that objective of providing guidance. Also, ll. 171-181 seem more related to scope than objective.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	7	208-210	All of these guidance references are from books, but the sentence refers to "articles". Independently from these books are guidances from journal articles, which are noted subsequently in the document, that should be considered as well. Perhaps the sentence should be "... original articles cited in these texts ... ."	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	8-9	213-262	It should become clear from the text what is mentioned with terminology such as 'effect modifiers', 'prognostic variables', 'confounders', 'confounding bias', …etc. Important to make a clear distinction and to use examples to explain the differences. The above mentioned ISPOR paper provides definitions and graphical illustration of the concepts (Jansen et al, 2014, ViH)	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	10-12	Section 2: 263-325	It would be useful for EUnetHTA to discuss the role of RWE in JCA. RWE has become important for demonstrating effectiveness in the real-world setting, particularly to assess effectiveness in subpopulations, inform historical controls and address uncertainty; greater consideration of RWE is certainly an initiative of EMA.	

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				However, the guidance text states that observational data could be used only if IPD are available to allow for rigorous adjustment for confounding. Access to IPD from observational studies and RWE (i.e. registries) may not always be feasible nor ethical due to data privacy considerations, particularly in rare disease settings. Even in an NMA or other type of indirect comparison is done using data from RCTs, only variables reported in the studies can be used for adjustment for confounding, or sometimes the only available evidence for a comparator is from a single-arm trial. Is the Methodological Guideline implying that these data from published observational studies are never going to be considered as part of the evidence for indirect comparisons? What are the options if there is no evidence for a comparator in a PICO except for observational data or single-arm trials? What if the clinical trial for the intervention in the PICO is a single-arm trial because it was conducted in an area of high unmet need for example? Furthermore, there is also no discussion or guidance on the relevance of the locality of the RWE when/if it is used; should a SLR of non-randomized evidence be conducted? Lines 310-312 - use of "Problematic" to describe evidence networks: Describing methods used to connect disconnected networks as “highly problematic” simply because there is no gold standard does not seem appropriate. Instances of disconnected networks are	

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				likely to be a frequent issue, particularly given a potentially large set of comparators of interest to cover the 27 member states and the anticipated evidence packages for many ATMPs and orphan and oncology medicines. In these disease states often is it not ethical or feasible to conduct an RCT or, as in the case of oncology, many variations of standards of care exist which may have limited data. Furthermore, describing these analyses and types of evidence as 'highly problematic' is subjective and a value judgement which is outside of the scope of the Regulation. This language stands to potentially bias the future JCA assessors towards only one type of evidence (RCTs) and lead them to disregard or not consider other evidence sources – both are not appropriate as the totality of evidence should be considered for a thorough assessment. It certainly should be acknowledged that non-randomized evidence and disconnected networks have more limitations than RCTs and require certain assumptions (which could be demonstrated to hold), however, we suggest that the Methodological Guidelines softens the tone against non-randomized or disconnected evidence while still listing their required assumptions and limitations. More generally terms such as "highly problematic" (e.g. lines 298, 762-764), "controversial" (e.g. lines 318, 867), and "unreliable" (e.g., line 320) are used throughout the document and should be revised per the rationale provided here and in	

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				the general comments and Section 5 comments.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	13	327-332	Why do authors make a distinction between consistency and similarity? The document could bring more clarity on the terminology. Currently no guidance is provided on best practices to collect KOL input on relevant patient characteristics, prognostic factors and effect modifiers.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	16,19	478-479, 574-576	Bayesian methods. An additional difference between frequentist and Bayesian methods that is not mentioned in the document is the differences in interpretation of results (e.g. credible intervals)	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	21	612-613	Please replace "adjusted indirect treatment comparisons" with "anchored indirect comparisons" throughout the document as it is less ambiguous. Also, it would be better to define this term as early as possible in the document.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	27	784-789 (and all of page 28):	A newer method for estimating a propensity score is available - the Covariate Balanced Propensity Score (CBPS; see Imai, JRSS, 2013).	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	24	711-712	The testing of shifted hypotheses represents just one of many sensitivity analyses that could be undertaken to assess the robustness of the population adjusted indirect comparisons. It would be more valuable to present a number of clear recommendations with assessing the validity of population adjustment	

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				approaches (requiring a multi-faceted approach), to describe different levels of uncertainty in specific contexts and recommended further analyses which can be conducted to further explore the sensitivity of the results due to the uncertainty.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	24	686-694	Other methods for time-to-event data include: Royston-Parmar cubic spline models, restricted mean survival time, piecewise exponential models (Freeman et al. Stat Meth Med Res 2022), and the two-step parametric NMA approach introduced by Cope et al. (Res Synth Methods, 2020) This openness to emerging methods should apply in general across all NMA, not just time-to-event data. Methods are constantly evolving and acknowledgement of this should be added to the summary and/or conclusions sections.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	26	755-765	Section 5.3.4 mentions issues with using MAIC/STC as population-adjusted methods for comparisons of single arm trials and these being "highly problematic". The same wording is used to describe approaches using observational data requiring IPD for the comparator. The Conclusion section mentions, in reference to using methods for single-arm/disconnected studies etc., "...the certainty of the results provided by these techniques remains controversial." There is a risk that unanchored approaches for indirect comparisons with	

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				single arm trials could be dismissed, or not fully considered, based on the wording in the draft guidance. There is published methodological guidance on the use of these approaches and many published examples of using these approaches in the literature. Although, limitations and interpretation of the results need to be considered carefully, and the approaches used should be tailored to the evidence in each case, these are still considered valid approaches for many HTA agencies and international HTA societies.	
D4.3.2 – Guideline on comparators and comparisons	ISPOR	26,27	755-792	Population adjusted indirect comparison methods involving single arm trials, disconnected networks, or other non-randomized evidence do not necessarily require full IPD ifor all studies involved. Frequently they can be undertaken if IPD is available for at least one study. It is a common situation as the manufacturer does not often have access to IPD data from comparators, particularly for innovative medicines. Please clarify Please rephrase, as follows: Pairwise population adjusted indirect comparison methods involving single arm trials, disconnected networks, or other non-randomized evidence require access to full IPD for at least one study. Ideally, full IPD information is available for all studies in the analysis. However, in many situations this may not be available.	

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				Also, it is useful to add to the document that only when anchored indirect comparisons are not feasible unanchored comparisons can be considered. In these instances it is recommended that a thorough description of the limitations of the unanchored population adjusted indirect comparison is provided and steps taken to address them be included."	