ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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August 30, 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 consultations "**D4.3.1 Practical Guideline Direct and Indirect Comparisons", "D7.2 – Patient and Clinical Expert Guidance"**, and **"D7.3 – Stakeholder Patient Input Template for Joint Clinical Assessments (JCA)."** 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 evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally; nearly 20% (1 in 5) of our membership resides within the European Union. Members across our organization come from 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 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 of our Health Science Policy Council, with comments solicited from several of our membership groups, including our HTA and Patient Representatives Roundtables, Institutional Council, Rare Disease Special Interest Group, Patient-Centered Special Interest Group, Statistical Methods in HEOR Special Interest Group, Network Meta-Analyses Good Practices Report authors, and the Systematic Reviews in Cost and Cost-Effectiveness Studies Good Practices Report authors, and Clinical Outcomes Assessment (COA) Good Practices Report authors. 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 participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Nancy S. Berg
CEO & Executive Director
ISPOR

EUnetHTA 21 Public Consultation

Comments should be submitted not *later than* *30 August 2022, 23:59 CET*

D4.3.1 Practical Guideline Direct and Indirect Comparisons,
D5.2 JCA Assessment Report Template,
D7.2/3 Guidance and template for the interaction with patient representative, healthcare professional and other experts ***(please note this consists of four templates)***

Please use this form for submitting your comments and share your completed comment form to JCA_Secretariat@zinl.nl prior to the deadline (30 August 2022, 23:59 CET). When submitting your comment form, please include "**EUnetHTA 21 – Public Consultation – D4.3.1, D5.2.1 or D7.2/D7.3** in the subject line of your e-mail.
Please carefully read the principles for public consultation here, prior to your review, as these are binding for our process.

We kindly ask you to:

1. Submit one consolidated response per organisation; in a word-file
    a. PDF files will not be accepted;
2. Complete the first table; if this table is not completed, the input will not be considered by EUnetHTA 21;
3. Put each new comment in a new row;
    a. Please be clear about the context of your comment and if possible, provide a suggestion for rewording;
    b. Please consider the HTA Regulation (EU) 2021/2282 when reviewing the document and when you provide comments;
    c. Please consider the corresponding project plan when commenting. Comments that refer to matters out of the scope of the deliverable may not be considered by EUnetHTA 21.
    d. Please do not provide linguistic comments, as the document will undergo language editing prior to finalization;
4. Insert the page number and line/section number on which your comment applies. If your comment relates to the document as a whole, please put **'general'** in this column;
5. Provide a description of your comment as specific as possible and preferably also provide a suggestion for rewording. If you wish to draw our attention to published literature, please supply the full reference;
6. Add rows as needed.

NB: All comments received within the deadline of the consultation and following the correct format will be published on the website, together with the final deliverable. Only comments eligible for consideration will be answered by EUnetHTA 21. The answers will be made publicly available as well. EUnetHTA 21 may decide to rank the comments received on importance.

Please complete this table. If this is not completed, your comments will not be considered.

Name organisation & abbreviation	ISPOR – The Professional Society for Health Economics and Outcomes Research
Country	Headquarters is based in the USA, but nearly 20% (1 in 5) of our membership lies within the European Union.
Contact details (name & e-mail address) – *this information will not be published*	Kelly Lenahan – klenahan@ispor.org Richard Willke – rwillke@ispor.org

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Is your comment an editorial comment?
	Insert your name and organisation ***Please repeat in each row***	***Insert 'general' if it relates to the whole document*** ***Please don't put 'p' before the number***		***Please insert each new comment in a new row.***	***Please indicate with 'x' if your comment is an editorial comment.***
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	General		No information is provided on how to understand or use large confidence intervals in the context of NMA.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes	General		For any research synthesis involving direct and direct comparisons, it may be helpful to discuss the study population first. It is common that a meta-analysis includes multiple studies with different subpopulations with different baseline risks. When we compare multiple treatments, it is important to make sure that relative effects are derived from the same population, i.e.	

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	Research			comparing the counterfactual absolute effects if all subjects included in a research synthesis analysis were treated with a particular treatment versus that under another treatment. In addition, it is also important to specify which type of treatment effects are of primary interests: the (weighted) average of conditional (or study-specific) effects, or the marginal effect over all subjects include in the meta-analysis. It may implicitly produce systematic bias when we assume a specific scale of relative effects is transportable or transitive across population with different effect modifiers. For example, the commonly used assumption, that odds ratios are transportable, is not valid as shown in a recent controversy and debate based on 40,243 meta-analyses from the Cochrane Database of Systematic Reviews (https://pubmed.ncbi.nlm.nih.gov/34384876/ and https://pubmed.ncbi.nlm.nih.gov/34390790/)	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	7-13	3 General Considerations (127-413)	In addition to randomized trials, it is unclear whether JCAs can use results from single-arm trials, historical controls, and non-randomized multiple arm trials to strengthen the evidence synthesis.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	7	135-138	From the patient's perspective, it is difficult to trade-off relative treatment effects among multiple outcomes. In addition to relative effects, should treatment-specific absolute effects be also provided as additional information? In addition, pooled relative treatment effects are conditional effects (i.e. weighted average of trial-specific effects), generally not equal to the marginal or population-averaged effects. This is particularly an issue for non-collapsible effect measures such as the odds ratio or hazard ratio. Absolute effects for all outcomes over all studies included in a research synthesis are important for patients and caregivers to trade-off potential benefits and	

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				harms, while one cannot make such decisions based solely on relative effects. For pooling absolute effects, we understand that there is some debate on the risk of break randomization when some studies use unequal group size randomization. However, as long as we use a study-specific weight (as compared to study-treatment-specific weights) for all intervention groups within a study, there is no such risk of break randomization. One can easily validate this argument for a direct comparison meta-analysis.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	7-13	158-413	As pointed out in lines 212-217, effect modification depends on the scale on which the treatment effect is measured, it suggests that the assessment of exchangeability, similarity, homogeneity, and consistency also depend on the scale of effect measurement. However, it is unclear how to decide which relative effects to use in practice. For example, when the baseline risks are high, the choice of RR versus OR can lead to a substantial difference in the assessments of exchangeability, homogeneity, and consistency. It may be useful to advocate using multiple scales of effect measurements for those assessments, or to provide some guidelines on the choice of effect scales in practice.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	9	252-262	While the Q and I2 statistics are useful measure of heterogeneity, they also have some limitations. For example, I2 statistics can be influenced by a few outlying studies, robust version of I2 statistics based median rather than mean have been proposed (https://pubmed.ncbi.nlm.nih.gov/27167143/), and has been shown to perform better (https://pubmed.ncbi.nlm.nih.gov/29847495/). In addition, I2 statistics is not an absolute measure of heterogeneity (https://pubmed.ncbi.nlm.nih.gov/28058794/).	
D4.3.1 Practical Guideline Direct and	ISPOR – The Professional Society for Health	10	274-287	For the assessment of homogeneity, recent literature includes fixed effect (or the common effect) model, fixed effects model and random effects model. Should the guideline include discussions on fixed effects model, and	

Please add extra rows as needed.

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Indirect Comparisons	Economics and Outcomes Research			choices among the three models? Furthermore, should the guideline discuss the assessment and approaches for small study effect, publication and reporting bias? Right now, it seems to be completely ignored, although that may not be intentional.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	14-19	4 Methods Applicable to Direct or Indirect Comparisons (414-649)	In addition to methods mentioned in Line 426-434, bivariate generalized linear mixed models (BGLMM) have been frequently used in pairwise meta-analysis estimating marginal risk difference and relative risk, and meta-analysis of diagnostics tests. They are shown to perform better compared to traditional two-step approaches (https://pubmed.ncbi.nlm.nih.gov/21177306/). In the presence of double-zero-event studies, Peto and other traditional method should be avoided. Bayesian BGLMM and exact methods are recommended (https://pubmed.ncbi.nlm.nih.gov/30887438/), except when none of the included studies have an event in one or both treatment arms.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	14	444-455	DerSimonian-Laird (DSL) method has been shown to produce biased estimates with falsely high precision (https://pubmed.ncbi.nlm.nih.gov/24727843/). Thus results from the Knapp-Hartung method should not be compared with DSL method - it might be better to be compared with random effects model using the REML method.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	15	485-490	For the choice of prior information, particularly for the variance parameters, one may consider to use empirical distribution based on large number of CDSR meta-analyses (e.g. https://pubmed.ncbi.nlm.nih.gov/22461129/). Again, small study effect, publication, reporting bias should be discussed.	
D4.3.1 Practical Guideline	ISPOR – The Professional Society for	16	533-539	While the original method of Lumley [32] and the 'arm-based' NMA introduced by Hong et al. [26] make different assumptions, they can provide very similar goodness-of-	

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Direct and Indirect Comparisons	Health Economics and Outcomes Research			fit to the data, and thus should be considered as alternative or sensitivity analyses to the contrast-based NMA. Furthermore, for binary data, the contrast-based NMA primarily use OR as the scale of effect measure. However, OR is a non-collapsible measure, the (weighted) average of OR from multiple studies, although mathematically attractive and valid, do not have a good interpretation as it does not apply to any population or study. In addition, for NMA of binary data, Bayesian methods should be preferred over frequentist approach as the latter typically has convergence issues when dealing with >3 or 4 dimension of random effects for a generalized linear mixed model. Computing relative effects with a normal approximation and subsequently fit linear mixed model can have issues for rare outcomes as it involves continuity correction.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	18	609 – 614	In addition to AIC, BIC and DIC, it would be useful to discuss the recently developed WAIC and LOOIC statistics.	
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	20-25	5 Assessment of Population-Adjusted Methods (650-919)	It is unclear whether Bayesian methods are considered acceptable for population-adjusted indirection comparison.	
D4.3.1 Practical Guideline Direct and	ISPOR – The Professional Society for Health Economics	26-28	6 Assessment of Comparisons Based Upon Non-Randomised Evidence (920-	For the assessment of non-randomized evidence, we might want to mention some of causal inference methodology such as g-computation etc. and recently developed causally interpretable meta-analysis methodology.	

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Indirect Comparisons	and Outcomes Research		1028)		
D4.3.1 Practical Guideline Direct and Indirect Comparisons	ISPOR – The Professional Society for Health Economics and Outcomes Research	27	995-1000	In addition ATT and ATE, overlap weighting which mimics attributes of a RCT have received large attention recently. It might worth to mention it.	
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	6	119	We suggest amending this wording to “Patient and healthcare professionals provide important knowledge about the disease, treatment processes, treatment outcomes, adherence issues and unmet medical need.” - this wording indicates the additional areas they contribute to, and emphasizes that not only they “can”, but that they “should” provide such knowledge. There are several other places in this section where “can” is used, which could suggest something is optional. The necessity of patient involvement should come through in all the language used. The 2021 EU Regulation on HTA (Point 1 and Articles 11, 4, and 18.6), recommends using the phrases “shall/should”. L_2021458EN.01000101.xml (europa.eu)	
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	8	206-218	We agree that confidentiality is critical in the process. The Confidentiality section makes it very clear that documentations and communications are well kept and the JCA report remains confidential until published.	
D7.2 – Patient and Clinical Expert	ISPOR – The Professional Society for	8	206	We recommend that EUnetHTA takes the initiative to have a separate section for confidentiality for stakeholders involved (in this case, they are patients and	

Please add extra rows as needed.

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Guidance	Health Economics and Outcomes Research			healthcare professionals). This section will help inform that stakeholders' information will be stored safely and will not be released without further permission, which will ultimately promote involvement and engagement in HTA.	
D7.2 – Patient and Clinical Expert Guidance D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	8	207	We think it helpful to address confidentiality from the perspective of patients and healthcare professionals. Emphasizing such that information provided by patients, patient advocate groups, clinicians and other healthcare professionals is well kept and remains confidential unless otherwise indicated.	
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	9	243-367	We agree that the process of recruitment of stakeholders and external experts and further involvement should be clear and appropriate. We feel that the guidance makes the process very clear in this section.	
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	9	243	We recommend EUnetHTA considers adding a separate section at the beginning of this Section 4 Process where considerations about diversity, equity, and inclusion are emphasized. We believe that the process of stakeholder engagement should not only lay out the technical process of engagement, such as timing, documentation and dissemination, but rather advocate an open, transparent, diverse, inclusive and equitable environment throughout the engagement process.	
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes	9	244	Emphasizing that the process is transparent will facilitate information sharing among key stakeholders. We also believe having a section to address the inclusive and friendly environment will make sure all parties in the HTA process be respectful and accountable for their activities.	

Please add extra rows as needed.

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	Research				
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	11	313-317	You may be aware that EUPATI maintains a network of patient experts. It may be worthwhile for EUnetHTA to make reference to EUPATIConnect in this section and to liaise with EUPATI to investigate and efficient way for patient experts to be included in the database.	
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	11	319	It would be useful to provide an explanation of how the data are preserved and kept. A flowchart may be useful for describing the process covered in the SOP.	
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	13	384	It would be worthwhile to collect data on unmet medical needs when collecting stakeholder information.	
D7.2 – Patient and Clinical Expert Guidance	ISPOR – The Professional Society for Health Economics and Outcomes Research	16	406-407	We suggest amending this sentence to "... to adequately reflect patient and healthcare professional involvement the method and timing of involvement, as well as the extent to which patient and healthcare professional influenced the JJSC or JCA overall, should be described in the JSC or JCA report." We realize the inserted phrase is mentioned in the table, but feedback on the results of patient involvement has often been neglected in the past and should be emphasized here.	
D7.2 – Patient and Clinical Expert	ISPOR – The Professional Society for	25	539	It would be helpful to provide a definition for patient advocate or include patient advocate in the patient representative's definition.	

Please add extra rows as needed.

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Guidance	Health Economics and Outcomes Research				
7.3 Stakeholder Patient Input Template for Joint Clinical Assessments (JCA)	ISPOR – The Professional Society for Health Economics and Outcomes Research	3	66	We suggest adding a question about how the disease affects the quality of life of patients. We recommend including a VAS scale.	
7.3 Templates	ISPOR – The Professional Society for Health Economics and Outcomes Research	General to both templates		The templates provide a thorough introduction and overview, and the questions include detailed prompts. This can be very helpful to users, but it may be worthwhile to consider the tradeoff between detailed prompts and user-friendliness.	
7.3 Templates	ISPOR – The Professional Society for Health Economics and Outcomes Research	General to both templates		For the “Impact of the condition” section, it is notable that the term “quality of life” is not used. This may be worth adding to the prompts.	
7.3 Templates	ISPOR – The Professional Society for Health Economics and Outcomes Research	General to both templates		It would be helpful to provide a clear statement on the template regarding the confidentiality of information collected.	

Please add extra rows as needed.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Is your comment an editorial comment?
7.3 Templates	ISPOR – The Professional Society for Health Economics and Outcomes Research	General to both templates		Informing individuals how all the information collected from the template will be used would be beneficial. In particular, the inclusion of the summary section ("Summary and key messages") without additional information may raise concerns that only this section will be used or will be of primary interest.	

Please add extra rows as needed.