PT30

Navigating the New European Member State Coordination Group on Health Technology Assessment Quantitative Evidence Synthesis Guidelines

Pragya Shukla, MSc[1], Victoria Paly, MHS[2], Irina Proskorovsky, MSc[3] Luis Hernandez, PhD, MPH, MSc[2]

[1]Evidera Inc., Montreal, Canada, [2]Takeda Pharmaceuticals America, Inc., Lexington, MA, USA [3]Evidera Ltd., Madrid, Spain

Background and Objectives

- The establishment of a framework for the European Health Technology Assessment (HTA) process is gaining momentum.
- Following the release of the initial draft Implementing Act on Joint Clinical Assessments (JCA), the Member State Coordination Group on HTA (HTACG) has issued two pivotal guidance documents: "Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons"[1] and "Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons."[2]
- The methodological guidelines describe different methods for direct and indirect comparisons, such as pairwise meta-analysis, network meta-analysis, population-adjusted indirect treatment comparison, and the use of non-randomized evidence. They also address assumptions, strengths, and limitations associated with each method.[1] The practical guidelines provide details on implementation of these methods and specify reporting requirements for Health Technology Developers (HTD).
- These guidelines play an important role in addressing the population, intervention, comparator, and outcome (PICO) questions in JCAs.
- The aim of this work was to review and map these documents into a practical decision algorithm to inform JCA dossier preparation planning.

Methods

- We conducted a comprehensive review of the HTACG Quantitative Evidence Synthesis Guidelines on Direct and Indirect comparisons.
- Key criteria, methodological requirements, recommendations, preferences, and reporting requirements were identified and extracted.
- The extracted information was then used to construct a step-by-step flowchart for decision-making processes based on specific context and available evidence and presented in a simplified and accessible format.

Key Takeaways

- A rigorous systematic review of the relevant literature and evidence (e.g., external control arm) with explicit inclusion and exclusion criteria is a prerequisite before conducting any direct and indirect treatment comparison and must address the PICO-based research question (**Figure 1**).
- Randomized controlled trials (RCTs) are the gold standard for informing estimates of treatment effectiveness and should be used for evidence synthesis when possible (**Figure 2**).
- A list of potential effect modifiers and/or prognostic factors should be drawn up a priori (i.e., before the evidence synthesis is performed).
- A fundamental assumption for evidence synthesis (direct and indirect comparisons) is exchangeability, which should be investigated by assessing similarity, homogeneity and, for indirect comparisons, consistency.
  - If the assumption is violated, the results of the corresponding evidence synthesis are unlikely to provide a meaningful estimate of treatment effectiveness.
- If the similarity assumption is not met, methods for population-adjusted indirect comparisons might be considered, provided that the network is connected, and individual patient data (IPD) are available for some included trials.
- With non-randomized data, such as observational evidence and single-arm trials, or in the case of disconnected networks, complete access to IPD is required to apply methods that can adequately adjust for confounding.

Figure 1. PICO Framework

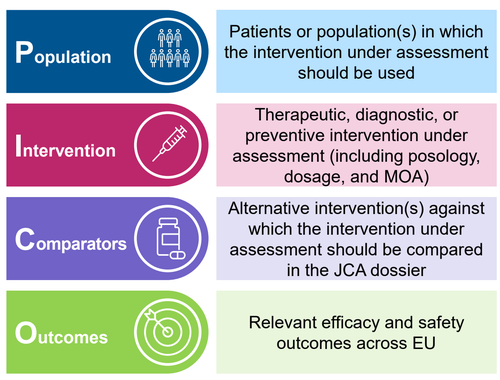
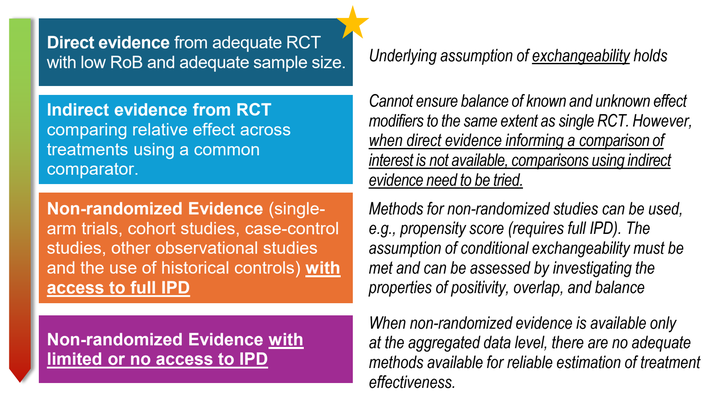


Figure 2. Hierarchy of Evidence

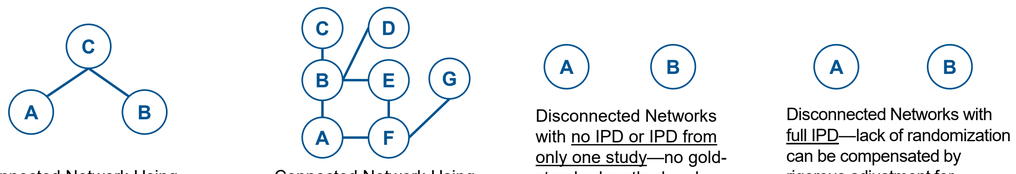


Roadmap for Direct and Indirect Comparisons

1 Assess Network of Evidence

- Evidence networks for indirect comparisons determine which methods are potentially applicable and should be constructed systematically from the PICO question(s) to avoid bias.

Figure 3. Different Types of Networks of Evidence



2 Identify and List All Potential Effect Modifiers and/or Prognostic Factors

- A list of potential effect modifiers and/or confounders should be drawn up a priori (i.e., even before the evidence synthesis is performed), and the process should be comprehensive and transparently reported.
- The process should include a comprehensive review of the literature and consultation with healthcare professionals (statistical tests should not be used in isolation to justify the selection).
- The set of all identified, potentially relevant effect modifiers and/or confounders should be reported in the submission dossier.
- Unavailability of data on a relevant effect modifier and/or confounder from one or more studies should be clearly reported as a limitation in the JCA report.
  - Possibility to consider proxies for the missing effect modifier in the assessment of similarity (sufficient evidence is needed to validate the proxy).

3 Check Assumption of Exchangeability

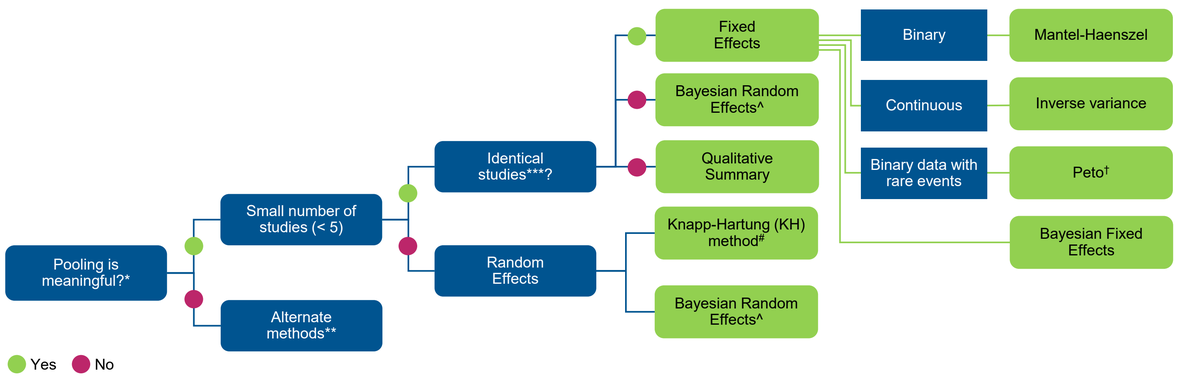
Table 1. Exchangeability Assumption

Testing the Assumption	What if assumption fails?
Similarity: • Assess the similarity of following aspects: – Study and patient characteristics (effect modifiers and prognostic factors) – Characteristics of the intervention and the comparator (dosage, application, and concomitant treatments) – Characteristics of outcomes – Observed values of relevant outcomes at baseline **Homogeneity:** • Heterogeneity can be clinical, methodological and statistical • Q statistic (Q-test), heterogeneity measure I^2, graphical inspection of forest plot **Consistency:** • Assess consistency of direct and indirect evidence by: – Bucher's method (Frequentist; simple loop network) – Inconsistency models (Bayesian) – Node splitting methods (Bayesian)	• In case if at least one of the components of the exchangeability assumption is not valid, following alternative approaches can be used to answer the PICO question: – Splitting into subgroups – Use of (network) meta-regression – Exclusion of studies – Sensitivity analyses – PAIC (STC/MAIC/ML-NMR) • Subgroup analyses are often more useful than meta-regression, as they can help in targeting the right intervention for the right subgroup of patients. • Limitations and assumptions of each of these methods should be considered • These options could lead to formation of new networks, therefore, subsequent testing of assumptions might be needed

4 Select Statistical Method for Direct and Indirect Comparisons

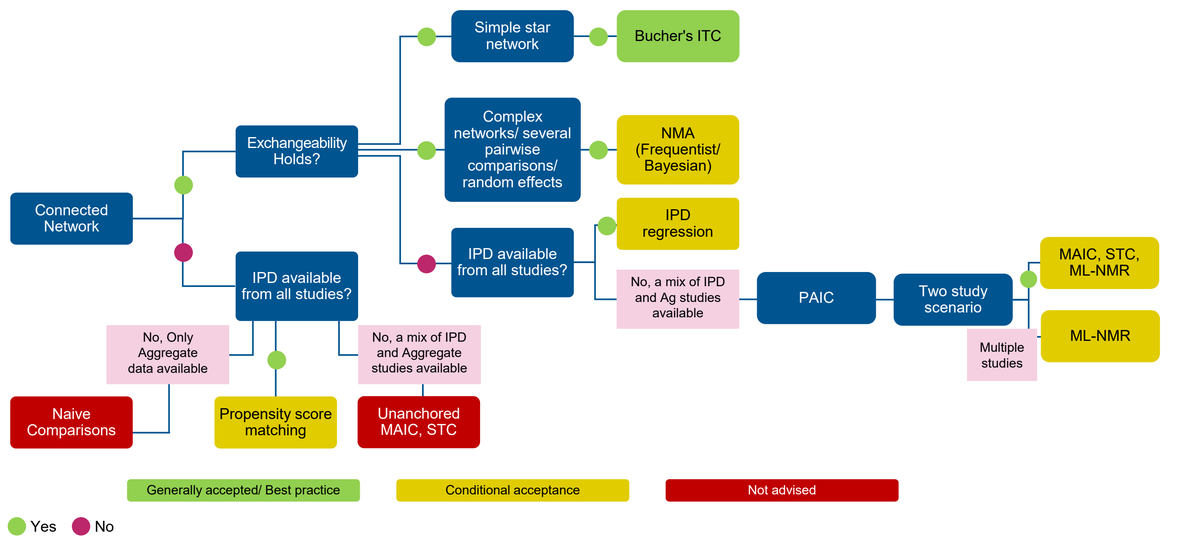
- Before undertaking any analyses, a statistical analysis plan is required.
- The following flowcharts can be used to select the appropriate method for direct or indirect comparisons.
- Not all methods for indirect comparisons are equally acceptable for JCA (refer to the color scheme). Assumptions associated with each method should be validated, and reporting requirements should be adhered to.

Figure 4. Methods for Direct Comparisons



*Assumption of exchangeability holds; **Alternative approaches to answering the PICO questions, for example: Splitting into subgroups, Use of (network) meta-regression, Exclusion of studies, Sensitivity analyses, Population-adjusted indirect comparisons (for indirect treatment comparisons); *** Studies are homogenous (similar study design and patient characteristics) and rigorous justification for the use of fixed effects is present. #In combination with the Paule-Mandel estimator for the heterogeneity parameter in situations with five or more studies. In practice, if the confidence interval of the Knapp-Hartung method is narrower than that of the DerSimonian and Laird method, the use of the ad hoc variance correction is required; †method should not be used when treatment effects are large, and the trial arm sizes are unbalanced; ^Guidelines recommend reporting prediction interval with random effects

Figure 5. Methods for Indirect Comparisons



Conclusions

- The proposed decision algorithm synthesizes HTACG guidelines for direct and indirect comparisons, serving as a valuable tool for researchers and practitioners. It enhances the transparency, consistency, and credibility of evidence synthesis, aligning with HTACG's emphasis on high-quality evidence.
- Additionally, the review highlights significant challenges that need to be addressed in the new HTA process, especially when the available methods for answering specific PICO questions are insufficient. This is particularly problematic for non-randomized evidence, especially in the context of single-arm trials and rare diseases.
  - Scoping and systematic literature review synthesis should start early to identify available evidence to allow HTDs sufficient time and budget for collecting and analyzing comparator data sources with IPD access, such as real-world evidence, registries, and chart review studies.
- While the guidelines outline several innovative and complex methodologies, they lack concrete implementation details in certain areas.

References

1. Member State Coordination Group on HTA. Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 2024; Accessible from: https://health.ec.europa.eu/document/download/4ec8288e-6d15-49c5-a490-d8ad7748578f_en?filename=hta_methodological-guideline_direct-indirect-comparisons_en.pdf
2. Member State Coordination Group on HTA. Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 2024; Accessible from: https://health.ec.europa.eu/document/download/1f6b8a70-5ce0-404e-9066-120dc9a8df75_en?filename=hta_practical-guideline_direct-and-indirect-comparisons_en.pdf

Abbreviations: Ag = Aggregate data; IPD = individual patient data; ITC = indirect treatment comparison; JCA = Joint Clinical Assessments; MAIC = matching-adjusted indirect comparison; ML-NMR = multilevel network meta-regression; MOA = mode of administration; NMA = network meta-analysis; PAIC = population-adjusted indirect comparison; PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial; RoB = risk of bias; STC = simulated treatment comparison

Acknowledgments: Editorial and graphic design support were provided by Michael Grossi and Richard Leason of Evidera, a business unit of PPD, part of Thermo Fisher Scientific.

Disclosures: This analysis was funded by Takeda Pharmaceuticals America Inc., Lexington, MA.
PS and **IP** are employees of Evidera, a business unit of PPD, part of Thermo Fisher Scientific, which was contracted by Takeda to conduct this study. **PS** and **IP** may hold stocks in Evidera. **VP** and **LH** are employees of Takeda and hold stock in the company.

Presented at the ISPOR Europe Conference, 17–20 November 2024, Barcelona, Spain. For questions or comments, please contact Victoria Paly: victoria.paly@takeda.com.