Should we Change our Approach to Conducting Indirect Treatment Comparisons for Joint Clinical Assessment? A Comparison with NICE Guidelines

HTA115

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INTRODUCTION

- **New EU regulation on health technology assessment (EU 2021/2282)** has been enacted since December 2021 and will come into force in January 2025 to "improve availability of innovative health technologies for EU patients, ensure an efficient use of resources and strengthen the quality of HTA".
- The regulation introduces a **Joint Clinical Assessment (JCA) of relative effectiveness** of products.
- The JCA is a **centralized European procedure to streamline and harmonize the assessment of health technologies across EU member states,** in which a single submission addressed both issues of relative effectiveness and relative safety.

OBJECTIVES

This study aimed to compare the recently published guidance documents:

- Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons and (1)
- Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons (2)

to the National Institute for Health and Care Excellence (NICE) health technology evaluation manual (3) and technical support documents to summarize key similarities and differences.

METHODS

The guidelines were contrasted based on the following components

1. Direct Comparisons, by means of pairwise meta-analysis
2. Indirect Comparisons, adjusted indirect comparisons including one common anchor treatment, and network meta-analysis (NMA)
3. Population adjustment methods, e.g., Matching-adjusted indirect comparison (MAIC), Simulated treatment comparison (STC), multi-level network meta-regression (ML-NMR)

RESULTS

The **Methodological Guideline** goes in greater detail about the mathematical and statistical foundations of ITCs and network meta-analyses (NMAs), providing in-depth discussions on the assumptions and technical aspects.

The **Practical Guideline is application-focused**, providing practical advice on how to implement the methodologies in HTA settings.

General Considerations

- A comprehensive and rigorous systematic review is a prerequisite before any evidence synthesis.
- **Evidence from randomised-controlled trials (RCTs) is considered the gold-standard**, however if non-randomised data are to be used, access to individual participant data (IPD) is required to apply methods that adjust for confounding.
- When multiple Population, Intervention, Comparator, Outcomes (PICOs) apply, a separate evidence synthesis per PICO is needed.
- A statistical analysis plan (SAP) pre-specifying the methods for evidence synthesis is required.

Direct Comparisons

The **JCA guidance** documents advocate the use of **frequentist** approaches for pairwise meta-analyses (MAs) between direct comparisons:

- Mantel-Haenszel for fixed-effect analysis of binary data with rare events
- Knapp-Hartung correction method for random-effects MA when there are ≥ 5 studies

Similarly to the NICE TSD, for MAs under the Bayesian framework, the use of non-informative priors is preferred. In cases of rare events, a weakly informative prior for the heterogeneity parameter is warranted.

Indirect Comparisons

- All guidelines require that the **exchangeability assumption** needs to be **thoroughly investigated** in any ITC
  - For direct evidence: via the similarity and homogeneity assumptions
  - For indirect evidence: via the consistency evaluations

Table 1. How to assess similarity and homogeneity under the JCA guidance

Similarity	Homogeneity
Present and compare study and patient characteristics, per treatment comparisons	Select between a fixed-effect and random-effect model, depending on number of studies and identified clinical heterogeneity
Present and discuss characteristics of interventions, i.e., dosage, regimen, mode of administration	• Use the revised classification criteria of I^2 metric: o 0–40%: might not be important; o 30–60%: might represent moderate heterogeneity; o 50–90%: might represent substantial heterogeneity; o 75–100%: considerable heterogeneity
Present and compare the characteristics of outcomes and observed values of relevant outcomes	Perform subgroup analyses and meta-regression, if homogeneity does not hold

For indirect comparisons with time-to-event data, the JCA guidance documents favor a **restricted mean survival times** approach over flexible survival models (advocated at NICE guidelines), **when the non-proportional hazard assumption does not hold.** Irrespective of the method used, prerequisites and assumptions related to the method must be clearly specified and justified.

Population adjusted methods

- JCA and NICE guidelines (TSD 18) agree that the **validity** of all population-adjusted methods depends on the **inclusion of all effect modifiers as covariates** in the relevant model.
- The practical guidance (2) states that MAIC and STC are suitable for exploratory analyses due to multiplicity issues, arising from "researcher degrees of freedom".
- **Transparent reporting of model selection** must be pre-specified in the protocol and SAP of the study to **mitigate the risk of selective reporting** as much as possible.
- ML-NMR has some conceptual advantages in facilitating inferences from larger networks with any number of treatments.
- Across all methods, the target population for which the treatment effect is estimated via a population-adjusted method has to be described in detail.

CONCLUSIONS

While the alignment between JCA and NICE is promising, context-specific differences necessitate careful planning for analyses to meet requirements in an efficient manner. An updated NICE TSD incorporating recent methodologies could further bridge these gaps.

REFERENCES

(1) Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons Adopted on 8 March 2024 by the HTA CG pursuant to Article 3(7), point (d), of Regulation (EU) 2021/2282 on Health Technology Assessment

(2) Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons Adopted on 8 March 2024 by the HTA CG pursuant to Article 3(7), point (d), of Regulation (EU) 2021/2282 on Health Technology Assessment

(3) NICE health technology evaluations: the manual NICE process and methods Published: 31 January 2022 Last updated: 31 October 2023 www.nice.org.uk/process/pmg36

DISCLOSURES

KP, PLN, MR, and AG are employees of Amaris Consulting. Authors have no conflict of interest to declare.

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