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Similarity of guidelines for direct and indirect comparisons under EUnetHTA and country-specific HTA – implications for supportive agents

Objectives

To ensure an assessment process of highest quality, the proposed guidelines of the European Network for Health Technology Assessment 21 (EUnetHTA 21) have been assembled based on input from various HTA bodies of the member states. However, it is unclear to which degree these guidelines overlap with existing and presumably differing guidelines from the member states and if recommendations from particular member states are better represented. This induces some uncertainty for pharmaceutical companies regarding the assessment and acceptance of some methods. Our aim was to identify similarities between the EUnetHTA 21 guidelines and guidelines from EU member states regarding direct and indirect comparisons. We choose Germany as an example since the German HTA was strongly involved in the design process of EUnetHTA 21. The degree of overlap between national and EUnetHTA 21 guidelines might suggest future implications for the national decision-making process when recommendations of the EUnetHTA 21 are provided to the national bodies.

EU Statistics similar to German HTA?

Methodology

We listed recommendations for direct and indirect comparisons presented in the practical and methodological guidelines of the EUnetHTA 21 (D4.3.1/D4.3.2) [1,2]. In a qualitive approach, we compared these recommendations to those stated in the method paper version 7.0 of the German HTA advisory body (IQWiG) [3].
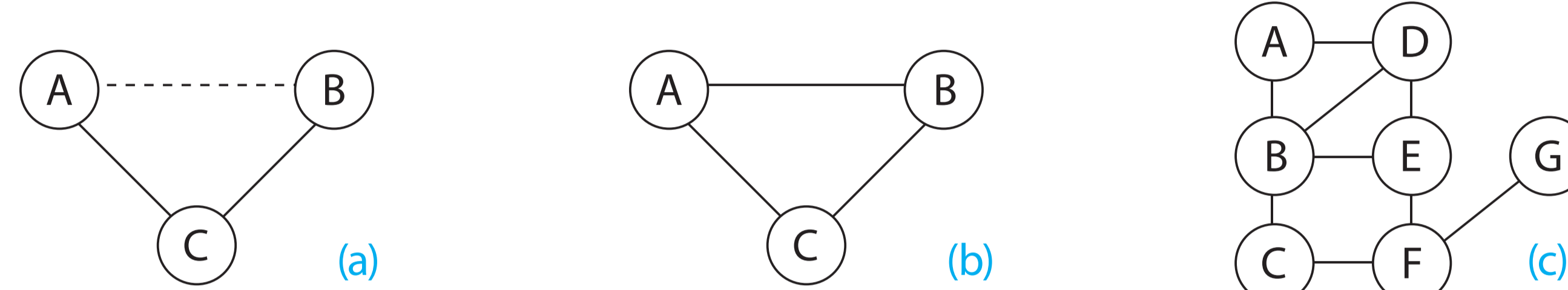
(a) Indirect comparison: RCTs comparing (A) to (C) and (B) to (C) (direct evidence), which then allows an indirect comparison (dotted line) between (A) and (B) , (b) Direct comparisons between (A) and (B) , (A) and (C) , and (B) and (C) , (c) network containing evidence for many different treatments, which allow many indirect comparisons between two treatments to be performed [2].

Results

Direct Comparisons

We found a high degree of similarity between the proposed EuNetHTA 21 guidelines [1,2] and the recommendations of the IQWiG method paper [3] (Table 1). Basically, recommendations of both guidelines overlap strongly with regard to direct comparisons. Recommended methods, rules-of-thumb and even citations in the documents are similar. Only with regard to the zero-cell correction and the application of DerSimonianLaird estimator in sensitivity analysis differences are visible. Especially, approaches for zero-cell corrections in contingency tables show some agreement but additional methods are mentioned in both guidelines. Perhaps in future adjustments of the guidelines this will be harmonized.

Table 1. Methodological recommendations of EUnetHTA 21 and German HTA for direct comparisons.

What	EUnetHTA 21	German HTA	Similar
Methods for fixed effects	Inverse Variance	Inverse Variance	✓
Application of random effects	If number of studies ≥ 5	If number of studies ≥ 5	✓
Heterogeneity measure for Knapp Hartung	Paule Mandel	Paule Mandel	✓
Methods for Sensitivity Analysis	Bayes	DerSimonianLaird	✗
Methods for Zero-Cell Correction	Avoidance, BetaBinomial, continuity correction	Avoidance, BetaBinomial, exact methods, Arc-sinus transf., Risk-difference	(✓)

Indirect Comparisons

The degree of similarity between the proposed EuNetHTA 21 guidelines [1,2] and the recommendations of the IQWiG method paper [3] was lower for indirect comparisons (Table 2). Both agree on the necessary assumptions (Table 2) to carry out indirect comparisons. However, while EUnetHTA 21 is more open to different approaches, such as population-adjusted methods (MAIC, STC, Propensity score matching), the German HTA does not encourage these methods. To our knowledge no MAIC or STC has ever been approved. These are usually not accepted because the above-mentioned assumptions are regularly not met and dramatic effects are missing. Second, unanchored indirect comparisons are not disregarded by EUnetHTA 21 if there are good reasons for an application. The German HTA accepted only very few unanchored comparisons which makes it unlikely that many cases will get approval in the future. Both guidelines recommend the Bucher method as a gold standard and Network Meta-Analysis as another valuable approach for conducting indirect comparisons with a single or multiple comparators. Yet, the German HTA complains that for NMA there is a lack of standardization (IQWiG) [3]. From our own observations we find that the Bucher method is the only accepted method by the German HTA for indirect comparisons [4]. It is therefore questionable how recommendations of EUnetHTA 21 will be handled by German HTA.

Table 2. Methodological recommendations of EUnetHTA 21 and German HTA for indirect comparisons.

What	EUnetHTA 21	German HTA	Similar
Assumptions	Similarity, Homogeneity, Consistency	Similarity, Homogeneity, Consistency	✓
Indirect comparison	Bucher Network-MA	Bucher (Network-MA)	(✓)
Population-adjusted indirect comparisons	MAIC, STC, Propensity Score matching	Requires IPD, until today no accepted cases	✗
Unanchored indirect comparisons	Possible, if dramatic effect	Requires IPD, but rarely accepted	✗

Conclusion

- In general, EUnetHTA 21 guidelines show high degree of similarity regarding the methodology of direct and indirect comparisons with the Germany HTA.
- Direct comparisons using fixed and random effect models are handled equally but differ in terms of sensitivity analysis.
- Indirect comparison using Bucher is currently the only regularly accepted method of the German HTA.
- EUnetHTA 21 might accept a larger spectrum of methods including MAIC or STC.
- It is likely that benefit assessments done by EUnetHTA 21 will improve the acceptance rate of indirect comparisons and that the national bodies will follow recommendations given by EUnetHTA 21.

References

[1] EUnetHTA 21 - Individual Practical Guideline Document, D4.3.1 Direct and Indirect Comparisons, Version 1.0, 16.12.2022,

[2] EUnetHTA 21 - Individual Practical Guideline Document, D4.3.2 Direct and Indirect Comparisons, Version 1.0, 29.07.2022,

[3] IQWiG – Allgemeine Methoden, Version 7.0, published 19.09.2023, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Köln, URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf

[4] Ecker T, Kandola S, Marx E, Brozek A, Ahrens L, Ritz-Jansen K (2023) Implications of EU HTA on Acceptance of Indirect Comparisons in National Assessments. ISPOR 2023, Boston, MA, USA.