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# Implications of EU HTA on Acceptance of Indirect Treatment Comparisons in National Assessments

## Objectives

Acceptance of indirect treatment comparisons (ITC) is one key challenge in HTA. The upcoming European HTA will set new standards on the European level. Hence, recently published method guidelines by EUnetHTA 21 on ITC might have an impact on national appraisal. This study analyzes (1) the current problems in accepting ITCs in (national) HTAs, (2) what methods are set out by EUnetHTA 21, and (3) the implications for upcoming national assessments post 2025. German HTA will be analyzed here, as it can be considered one of the most rigorous national HTA within the EU.

## Methods

All ITCs are identified by screening German HTA body (G-BA) justification of resolutions since 2011 and up to March 2023, excluding orphan drug assessments, by using the following German keywords *"adjustiert", "indirekt", "historisch", "Netzwerk", "dramatisch", "Fallkonstellation"* (adjusted, indirect, historical, network, dramatic, case constellation). Reasons for acceptance or non-acceptance are extracted and categorized (rejection categories: 1. aspects relating to the method of the ITC (e.g. choice of method, incomplete information retrieval, heterogeneity), 2. exchangeability assumption violated (e.g. insufficient similarity regarding study population, endpoints), 3. study not appropriate (e.g. inadequate study duration, comparator), 4. unclear (no clear reasoning provided)). More than one reason can apply to one assessment. One assessment can comprise more than one ITC; they will be counted separately. European HTA standards on ITCs are extracted from recently published guidelines by EUnetHTA 21[1,2] and compared to the German standard.[3]

## Results

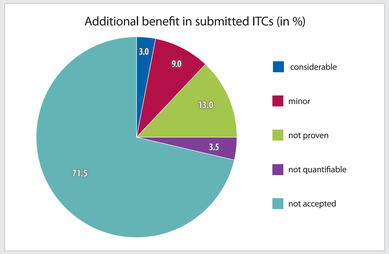


**Figure 1:** Distribution of additional benefit per submitted ITC in %. No ITC led to a major additional benefit.

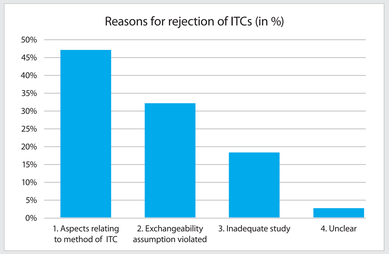


**Figure 2:** Reasons for rejection of the ITCs in % in relation to all given reasons.

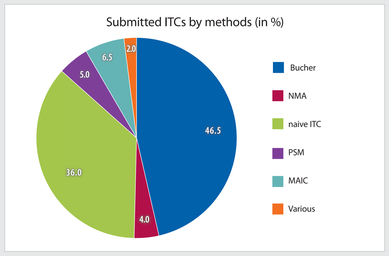


**Figure 3:** Distribution of submitted ITCs by method in %.
(NMA: network meta-analysis, PSM: propensity score matching, MAIC: matching-adjusted indirect comparison).

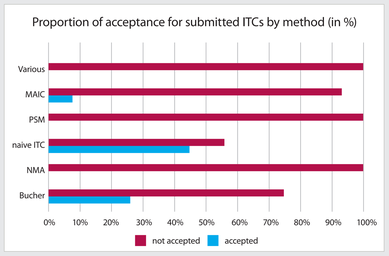


**Figure 4:** Proportion of acceptance for submitted ITCs by method in %.

- In total 620 assessments have been screened. In 140 assessments ITCs have been submitted. In some assessments more than one ITC has been submitted resulting in 200 ITCs in total.
- Most ITCs have been submitted for medicinal products in the therapeutic area of oncology (44.5 %), infectious diseases (19.0 %) and metabolic diseases (11.5 %).
- Only 28.5 % (57/200) of submitted ITCs have been accepted by G-BA (Figure 1), with the majority providing only supplementary evidence.
- 71.5 % (143/200) ITCs have been rejected by G-BA due to different methodological reasons. Common reasons for rejection were the choice of method, an inadequate implementation of the method and violation of the similarity assumption (Figure 2). However, G-BA is usually short on details of specific aspects.
- The Bucher method has predominantly been applied (46.5 %), which is the only method G-BA currently considers to be adequate (Figure 3). Nevertheless, of the submitted Bucher ITCs, 74 % have still been rejected (Figure 4). The relatively high number of accepted naïve (unanchored and unadjusted) ITCs can be attributed to exceptional cases (e.g. hepatitis assessments).

**Key messages on ITC based on EUnetHTA 21 guidelines[1,2]**

- In contrast to the "General Methods" paper by IQWiG[3], which provides the general framework for the German HTA, EUnetHTA 21 elaborates in detail in two distinct guidelines on methodological and practical considerations of ITCs.
- For instance, the guidelines provide precise recommendations on:
  - methodological options for different types of evidence
  - different methodological approaches in case the main assumptions for a high-quality ITC (i.e. similarity, homogeneity and consistency) are violated - especially for "similarity", which is often reason for rejection of ITCs in German HTA (e. g. anchored population-adjusted methods like MAIC or STC (simulated treatment comparison))
  - reporting requirements for an ITC to be adequately assessable
- Risk of bias plays a central role in ITCs and especially unanchored ITCs. Therefore, anchored ITCs are highly preferred.
- Unanchored ITCs are also addressed in the guidelines and methodological recommendations are provided. Limitations in the context of assessing the absolute treatment effectiveness are clearly discussed.

## Conclusion

- In German HTA, the majority of indirect comparisons are rejected (71.5 %) due to methodological reasons. Predominantly ITCs using the Bucher method are accepted. Other methods or unanchored ITCs are only accepted in specific (exceptional) settings.
- The EUnetHTA 21 guidelines give a much-needed methodological clarity for ITCs. A more detailed guidance for assessing similarity, homogeneity, consistency and corresponding requirements for reporting, as well as recommendations on possible approaches and methods when the assumptions are violated is provided.
- As European HTA is intended to cover the requirements of all member states (i.e. in terms of comparator for the drug of interest), it is conceivable that ITCs will play a major role in the majority of assessments.
- It remains to be seen whether ITCs will be more widely accepted on European level and whether and how this will affect national HTA.
- It is expected that countries with a well-established national HTA may stick to their own assessment standards where possible to ensure procedural consistency. This holds true especially for the rigorous German HTA. However, accepted ITCs on a European level that are based on a high methodological and reporting standard may be difficult to reject on a national level.
- Hence, it would be very surprising to see an ITC being rejected on the national level due to methodological concerns, once it had been endorsed in the joint clinical assessment (JCA) report.

## 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 – General Methods, Version 6.1 of 24 January 2022, https://www.iqwig.de/methoden/general-methods_version-6-1.pdf