Similarities and differences between the HTA methods for indirect comparisons in the EU JCA and national assessments by Member States

HTA147

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Background

- The assessment of relative effectiveness and safety in the joint clinical assessment (JCA) is a fundamental aspect of the EU Health Technology Assessment Regulation (HTAR). Given the variation in clinical practice between Member States, direct comparative evidence is unlikely to be available for all comparators in the JCA scope.
- Therefore, indirect treatment comparisons (ITCs) will be a key source of evidence for relative effects in JCA submissions, which are covered by two methodological guidelines prepared by EUnetHTA21. This research aims to explore of the differences between the methods for ITCs to be used in the JCA and select Member States.

Objectives

- Review the methodological requirements for ITCs for selected EU Member States and the Joint Clinical Assessment.
- Identify areas of harmonisation and divergence in the methodological guidelines to understand how acceptable ITC methods vary within the EU.
- Identify possible areas of challenge in the applying methods for ITCs in the Joint Clinical Assessment and Member States' national processes.

Methods

- We conducted a targeted review of methodological guidelines from EU and European HTA bodies: the EU's EUnetHTA21[1], Germany's Institute for Quality and Efficiency in Health Care (IQWiG)[2], France's Haute Autorité de Santé (HAS)[3, 4], Agenzia Italiana del Farmaco (AIFA) from Italy[5], the Norwegian Institute of Public Health (NIPH)[6], and the Agency For Health Technology Assessment And Tariff System (AOTMiT) from Poland[7]. These bodies were selected to provide a range of approaches to HTA, population size and geographic location in Europe.
- The most recently available guidelines from each organisation were reviewed to identify areas of harmonisation and differences between EU and Member State HTA methods for ITCs. The reviewed guidelines are listed in the reference list below.

Results

Level of detail:

- Our review found differences in the level of prescriptive guidance. Germany and EUnetHTA21 provided the most prescriptive guidance, which included specific details for statistical testing and assessment of heterogeneity.
- Norway, Poland and Italy provided more descriptive guidance, and left the selection of statistical methods and description of assumptions to the health technology developer.

Accepted methods:

- ITCs are generally accepted. However, some guidelines only accept them in specific circumstances. For example, France and Germany only accept ITCs if there is appropriate justification for not conducting an RCT.
- Norway and Poland accept ITCs if a direct comparisons against a relevant comparator is unavailable. There were no apparent restrictions by Italy or EUnetHTA21.
- Use of pairwise ITCs and network meta-analysis methods is universally accepted. Unadjusted comparisons are not accepted by any HTA body.
- EUnetHTA21 requires patient-level data for comparisons in disconnected networks. Whilst Germany does not accept disconnected networks, this was not mentioned by other countries.

Population adjustment:

- Germany states that population-adjustment is unsuitable without exception.
- France states a preference for adjusting for confounders using methods that rely on individual patient data (IPD) such as propensity scores analysis, g-computation, and doubly robust estimation. Population-adjustment methods are sometimes accepted, but the reliance on the assumption of the conditional constancy of absolute effects is noted as a limitation.
- EUnetHTA21 considers population-adjustment only suitable as exploratory analysis, and considers methods that rely on IPD, namely propensity score analysis, as more appropriate.
- Norway and Poland allow submissions that use population-adjustment methods and provide guidance on methodological requirements.

Results

Table 2. Summary of methodological guidelines

	Methodological Consideration			
	Acceptance of ITC methods	Inter-trial heterogeneity	Population adjustment	Acceptance of non-randomised data
EU	Methods include Bucher's method for ITC, NMA, and population adjustment. Unadjusted ITCs are not accepted.	Guidance on assessing similarity, homogeneity and consistency. Guidance on statistical methods included.	Population adjustment only accepted as an exploratory analysis.	Accepted, but associated with bias. Requires IPD and pre-specified adjustment for confounding.
FR	Adjusted ITCs, NMA, mixed-linear model, meta-regression and Bayesian NMA are accepted. Preference for NMA methods.	Use trial subgroup analyses to identify effect modifiers. Measure inter-trial heterogeneity with a meta-analysis.	Population adjustment is sometimes considered. Preference for methods that use IPD versus STC and MAIC.	Accepted, especially for rare indications. Use of non-randomised data requires the availability of IPD.
DE	Requires 'adequate justification', accepts adjusted ITCs or NMA. Unadjusted ITCs are not accepted. Use blinded, RCTs with an active comparator.	Provides guidance on the measurement of heterogeneity.	Population adjustment not accepted.	Rarely accepted due to the lack of randomisation and sufficient data on risk factors to adjust for confounders.
IT	No restrictions, but a full description of methods and assumptions required.	Not discussed.	Not discussed.	No restrictions, multiple data sources accepted.
NO	Matched-pairwise ITCs, NMAs and other valid methods accepted. Unadjusted ITCs not accepted. Quantitative and qualitative evaluation of the risk of bias.	Known effect modifiers and prognostic factors must be described as fully as possible from previous knowledge.	STC and MAIC are referenced in the guidelines, with a minimum set of methodological criteria required.	Accepted, data source quality, study design, patient characteristics, and statistical considerations must be provided.
PL	Adjusted ITCs, Bucher, logical regression or meta regression are recommended; NMA can be used if justified.	Tabulated summary of the inter-trial differences between populations and endpoints.	Methods for population adjustment are not described.	Not discussed.

Discussion

- In contrast to most EU Member States, EUnetHTA21 guidelines provide prescriptive guidance on the methods for indirect comparisons. While they do not place restrictions on the circumstances where ITCs are accepted, they fail to recognise situations where alternative methods may be required, such as new indications, rare disease, or high unmet needs. Consequently, there is a risk of these guidelines preventing assessors from making context-dependent decisions on the appropriate evidence.
- EUnetHTA21's requirement for connected networks also presents some challenges. Due to a potentially large number of comparators in the JCA scope, it may not be feasible to develop a connected network for all comparators. This may be further complicated by health technology developers not having access to IPD for comparator trials.
- To proactively address these challenges, health technology developers can elect to engage in early dialogues/scientific advice with HTA bodies, including Joint Scientific Consultations, to validate potential ITC approaches in the context of specific health technologies and indications. However, developers may not always be eligible for these procedures and should identify a full range of formal and informal scientific advice engagement options in Europe as they plan Joint Clinical Assessment (JCA) submissions.

Conclusions

- Our review identified areas of harmonisation, including a preference for direct comparisons and methodological approaches for ITCs. However, given the methodological divergence between Member States, reaching methodological guidelines by consensus is challenging.
- The current guidelines for EU HTA limit the feasibility of ITCs to provide evidence for relative effectiveness for JCA submissions and currently offer limited pragmatic solutions to meet the objectives of EU HTAR and ensure appropriate and timely access for EU patients.
- Further research is required to understand how EUnetHTA21 guidelines will be interpreted by different assessors at the time of a JCA, especially for unique circumstances where alternative methods may be accepted by HTA bodies at a national level.

References

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