Comparison of the Guidelines for Quantitative Evidence Synthesis in the European Union (EU) Joint Clinical Assessment (JCA) of medicinal products to current methods for Health Technology Assessment (HTA) in Germany

HTA379

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OBJECTIVES

Commencing 2025, new oncology medicines and advanced therapy medicinal products will be assessed at the EU level. The EU Coordination Group on HTA recently published methodological and practical guidelines for evidence synthesis in terms of JCA, which were developed in close collaboration with German healthcare authorities.

Here, we compared the published guidance for JCA with the HTA methods used by German authorities. Each local HTA authority can demand additional evidence beyond what is covered by the JCA dossier in so-called delta dossiers. To anticipate the workload for such dossiers, it is important to know where the current local methodological requirements differ and are more prescriptive compared to JCA requirements.

METHODS

The European Methodological and Practical Guidelines for Quantitative Evidence Synthesis for JCA [1,2], on one side, and the General Methods published by the Institute for Quality and Efficiency in Health Care (IQWiG) [3] as well as the Rules of Procedure by the Federal Joint Committee (G-BA) for AMNOG [4], on the other side, were compared to each other.

Notable differences between the current AMNOG methodology and the proposed JCA approach were listed and presented in Table 1. The more prescriptive requirements were highlighted in red.

RESULTS

The general approach for evidence synthesis is largely congruent between JCA and AMNOG methodology. However, JCA requires a more thorough documentation than AMNOG regarding the fulfilment of the exchangeability requirements and how apparent failures to meet them are addressed, the plausibility of the underlying model assumptions, and the estimation of effect measures.

For direct comparisons, the guidance is largely congruent between JCA and AMNOG. Both show a strong preference for direct treatment comparisons over indirect approaches, even if the comparison is made via a common comparator.

However, if only indirect comparisons can be shown, JCA and AMNOG differ in their specifications as to what constitutes an appropriate methodology. For AMNOG, anchored comparisons and an adequate connecting comparator are required. Unanchored indirect comparisons are not accepted for AMNOG but are mentioned as a possibility for JCA. AMNOG considers indirect comparisons without common comparators only if full individual patient data (IPD) are made available for all trials, whereas JCA mentions that IPD from a single-arm trial can be used in addition to aggregated data. However, neither authority fully endorses this approach as acceptable explicitly.

Nonetheless, even if the strict requirements are met, in AMNOG, any acceptance of an indirect comparison to determine an additional treatment benefit generally requires the demonstration of dramatic treatment effects.

Table 1 – Overview of key differences between JCA and AMNOG guidance

Direct Comparison		
Topic	**JCA (EU Coordination Group on HTA / MPG)**	**AMNOG (G-BA/IQWiG)**
Identification of effect modifiers for similarity and evaluation of homogeneity	Requires the **consultation of HCP and literature reviews** for the identification of effect modifiers and **specific statistical measures** for the evaluation of homogeneity	**Does not specify** which methods to use for identification of effect modifiers and evaluation of homogeneity or interaction testing
Consistency testing	Requires **specific methods** for the choice of consistency test	IQWiG acknowledges that consistency testing **cannot always be done**
Frequentist approach in direct comparisons – zero cases	Proposes alternatives to avoid necessity for zero-cell correction	IQWiG requires a **specific method** for correction of zero cases
Indirect Comparison		
Topic	**JCA (EU Coordination Group on HTA / MPG)**	**AMNOG (G-BA/IQWiG)**
Appropriateness of indirect comparison	Proposes **alternatives** if no anchored comparisons are possible (e.g., unanchored STC and MAIC depending on available data)	Only allows **anchored ITC**, preference for Bucher method
Common comparator	No defined limitations; complex or disconnected networks possible	Only allows **first-degree common comparators**
Network meta-analysis (NMA)	Option to present **Frequentist, Bayesian, or a range of other NMA methods**	NMA are acceptable in principle, no mention of specific methods beyond Bayesian NMA
Disconnected networks / non-randomised evidence	When IPD from a single-arm trial and aggregated data are available, unanchored STC and MAIC have been proposed. If full IPD information for all relevant co-variates (confounders; prognostic variables or effect modifiers) is available, analyses with adjustment for confounding can be performed.	Do not perceive MAIC as adequate method for confounder adjustment; instead require methods based on complete IPD information

More prescriptive requirements highlighted in red

DISCUSSION & CONCLUSION

Comparing the methodologies published for JCA and AMNOG, relevant differences in the requirements for presenting indirect treatment comparisons were identified. In Germany, only anchored indirect comparisons are generally accepted and with demands of providing IPD in the case of no common comparator. In general, the chances of an indirect comparison being accepted in AMNOG are considered very low, as the benefit assessments for e.g., pembrolizumab [5,6] and etranacogen dezaparvovec [7] have shown.

In the light of the generally more prescriptive requirements set out by the German authorities, it remains to be seen to what extent they will accept the evidence presented in the JCA dossier to assess the additional benefit of a medicinal product in the context of AMNOG. As the JCA is not legally binding, the G-BA may request additional analyses from the health technology developer that go beyond the JCA dossier and that will have to be provided in the form of a local delta dossier. The practical implications of the identified differences for the delta dossier must be evaluated once the first JCA submissions have been assessed.

References:
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Abbreviations: AMNOG: Arzneimittelmarktneuordnungsgesetz [German Medicines Market Reorganisation Act]; CG: Coordination Group; EU: European Union; G-BA: Gemeinsamer Bundesausschuss [Federal Joint Committee]; HCP: Healthcare professional; HTA: Health Technology Assessment; IPD: Individual patient data; ITC: Indirect treatment comparison; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care]; JCA: Joint Clinical Assessment; MAIC: Matching-adjusted indirect comparison; MPG: Methodological and Procedural Guidance Sub-Group; NMA: Network meta-analysis; STC: Simulated Treatment Comparison; TTE: Time-to-event

Poster presented at ISPOR Europe 2024 on 20th November 2024; Presentation Code: HTA379
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