European Access Academy

EAA Commentary on the Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

The HTA Coordination Group (CG) adopted on 8 March 2024 new Guidelines for HTA CG pursuant to Article 3(7), point (d), of the Regulation (EU) 2021/2282 on Health Technology Assessment.[1] The guideline is an adaptation of the European Network of Health Technology 21 (EunetHTA21) Methods guideline 4.2.3 on direct and indirect comparisons (**Version** 1.0, 29.07.2022) and with regard to its content largely congruent with the EUnetHTA21 guideline. The objective of the guideline "is to describe the methods currently available for direct and indirect treatment comparisons regarding their underlying assumptions, strengths, and weaknesses."

A key feature of the EU HTA regulation and the recently published Implementing Act on 'Joint Clinical Assessment' is the definition of the Assessment Scope Proposal. Multiple PICO (Population/ Intervention/ Comparators/ Outcomes) schemes are expected for each of the assessments. The respective pilot PICO exercise by EUnetHTA 21 including three medicines (Pluvicto®; Ebvallo®; Pombiliti®) revealed 5-9 PICOs per assessment. However, this pilot exercise included only 8-10 of the EU Member States[2], so a further increase of the number of PICOs has to be expected when taking into account all 27 EU Member States. Furthermore, it has not been researched by the EUnetHTA21 group what data are available to support any of the identified PICOs.

Against this background, and also taking into account the shift in research paradigms towards ever smaller and more targeted treatments in small patient populations, it is obvious that indirect treatment comparisons will be a key – if not dominating – feature in any upcoming EU HTA assessment. Availability of RCT data derived from the clinical development program might serve 1 or 2 PICO schemes per assessment, with all other schemes to be supported by indirect evidence. Many suggested PICO schemes may cover distinct populations or treatment pathways that reflect past standards of care. Therefore, the request for preservation of randomisation in ITCs i.e., conduct of anchored indirect comparisons and the prerequisite of the availability of Individual Patient Data to conduct further analyses as stipulated in the CG guidance will frequently be impossible to fulfill. Available networks for indirect comparison will often be 'asymmetrical' and 'incompletely saturated' relying on observational, 'real world' data.

A recent review of 111 indirect comparisons that were provided in 62 German HTA assessment revealed a rejection rate of 94% by the German HTA Body IQWIG. Key rationales for rejection were applicability of study design (47.7%); comparability of study characteristics (39.6%), and completeness

[1] https://health.ec.europa.eu/document/download/4ec8288e-6d15-49c5-a490-d8ad7748578f_en?filename=hta_methodological-guideline_direct-indirect-comparisons_en.pdf
[2]https://www.ispor.org/docs/default-source/euro2023/ispor-session-101---anne-willemsen-handout.pdf?sfvrsn=11194ce5_0

of study data (38.7%), statistical features (25.2%), comparative therapy (8.1%), and homogeneity/ consistency (2.7%).[3]

In order to further develop the methodology applicable for indirect comparisons in the evolving EU HTA procedures the EAA faculty kindly suggests that the Coordination Group should further substantiate the underlying evidence base of their methodological guidance:

- *Revisiting the 3 EUnetHTA 21 pilot PICOs (Pluvicto®; Ebvallo®; Pombiliti®) leveraging two research questions:*
    - *how many PICO schemes are required when including all 27 EU Member States instead of only 8-10 Member States*
    - *reflecting the existing body of evidence: which of the identified PICOs could have been supported with existing RCT evidence and/or with existing anchored indirect evidence based on Individual Patient Data*
- *Specifying criteria when the conduct of an RCT is not feasible and/or not ethical.*
- *Specifying criteria when the development of anchored indirect evidence and/or the provision of Individual Patient Data (e.g., for past standard of care treatments) is not feasible.*
- *Specifications for which comparisons evidence from non-randomised external control-based methods may be accepted and specification of methods for such comparisons. Thereby specifying ITC acceptability thresholds that are taking into account the uncertainty of ITCs and the related increase in required effect size. The current guideline has more of a focus on standards of reporting for evidence synthesis.*
- *Specifications for validity criteria of indirect comparisons from evidence synthesis of indirect comparisons, in particular for network meta-analysis.*

Considering the multiplicity and the heterogeneity of expected EU HTA PICO schemes the EAA Faculty strongly suggests to the Coordination Group to take a thoughtful and rational approach to 'Best Available Evidence', where the potential of comparative data is to be judged by clear explicit rules. Up front rejection of 'Best Available Evidence' based on criteria such as the lack of availability of Individual Patient Data or the lack of preservation of randomisation will lead to rejection numbers that are even higher than the 94% that were identified in the above-mentioned review of the ITC in the German HTA environment.

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[3] https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-0890-7985?device=mobile&innerWidth=412&offsetWidth=412&lang=de