Poster #PT29

From European Union Joint Clinical Assessments to Local Health Technology Assessments: An Environmental Scan of Methodological Guidance Across Key European Markets

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Background

- With the European Union (EU) Health Technology Assessment Regulation (HTAR) approaching implementation, health technology developers (HTD) must familiarize themselves with EU joint clinical assessment (JCA) requirements and understand how they interplay with national health technology assessment (HTA) processes.
- Member States must incorporate JCA findings into their HTA to ensure a unified approach across jurisdictions. However, they may also request additional analyses to meet specific national needs, highlighting the importance of flexible, adaptable evidence generation strategies.
- Identifying any HTA methodological differences across the EU is essential for HTDs to avoid redundant submissions, optimize evidence planning, and support efficient market access across diverse EU health systems.

Objective

- The aim of this project was to conduct an environmental scan of methodological guidance documents across the EU JCA including the European Network for HTA (EUnetHTA) and key European HTA agencies in Germany, France, the Netherlands, and Spain to assess their commonalities and differences.

Methods

- An environmental scan was performed to identify methodological guidance documents for scoping considerations, evidence identification and synthesis published by the European Commission, EUnetHTA, and four representative European HTA bodies.
- The websites of EUnetHTA, the European Commission, the Institute for Quality and Efficiency in Health Care (IQWiG), Haute Autorité de Santé (HAS), the Spanish Agency of Medicines and Medical Devices (AMEPS), the Agency for Health Quality and Assessment of Catalonia (AQuAS), and the Zorginstituut Nederland (ZIN) were searched in March 2024 and again in June 2024.
- A comparative analysis was conducted in which evidentiary requirements of EU HTAR were matched with those of the four representative European HTA bodies selected. This thematic analysis was conducted in three steps:
  1. Identification of the methodological guidance documents by each included agency
  2. Extraction of the evidentiary requirements from the EU HTAR grouped across three areas: scoping specifications, evidence selection, and evidence synthesis
  3. Summary of key EU HTAR considerations through qualitative statements and mapping of local HTA methodological guidance recommendations against these statements.

Results

- Thirty methodological guidance documents were identified (EUnetHTA and European Commission [n=12]; IQWiG [n=7], HAS [n=5], ZIN [n=4], AEMPS [n=1], AQuAS [n=1]).
- Guidance consistently emphasized randomized controlled trials (RCT) as the highest quality evidence; non-randomized studies could be considered in exceptional cases although HAS, ZIN, and AEMPS provided a wider range of acceptability criteria than IQWiG and EU HTAR.
- Alignment was found on the importance and the accurate reporting of clinically relevant endpoints and the need for a-priori specification of a statistical analysis plan. There was variability in the acceptance of surrogate outcomes.
- Although the EU HTAR considered the use of novel analytical ITC methods (e.g., ML-NMR) whereas other HTA bodies did not, strict criteria for unadjusted ITCs and evidence synthesis from non-randomized studies challenge their applicability in real-case decision problems.

Conclusions

- Several methodological differences were noted between the EU HTAR and local HTA methods guides with the closest alignment found between EU HTAR and IQWiG.
- HTDs need to anticipate the impact of these differences when developing evidence generation plans and exploring the impact on value stories for local submissions.
- Closer methodological harmonization between local European HTAs and EU HTAR would ensure smooth transferability of EU JCA to local settings without duplicated effort, though it remains to be seen how this will play out in "real" decision-making.

Results

Table 1. Commonalities and differences between EU JCA methodological guidance and key European HTA bodies

		EU HTAR[1,2]	Germany[3]	France[4]	Netherlands[5]	Spain[6,7]
Scoping specifications		Overall assessment scope should follow PICO framework and be inclusive of the needs of all 27 Member States	Only German needs	Only French needs	Only Dutch needs	Only Spanish needs
		EMA full label with subgroups of interest should be clearly defined (e.g., delays expected if CHMP opinion makes changes in the submitted indication)	Population does not always align with EMA label	Population does not always align with EMA label	Population does not always align with EMA label	Population does not always align with EMA label
		Detailed guidance about defining "comparator" (e.g., off-label treatments, background therapies, individualized treatment comparator)	G-BA defines the comparator	Available local clinical care	Available local clinical care	Available local clinical care, evidence from public clinical trials, off-label treatments
		Equal importance to effectiveness, safety, and quality of life outcomes	☑	☑	☑	☑
Evidence selection		An SLR with explicit inclusion and exclusion criteria (following PICO framework) is compulsory	☑	☑	☑	Some details
		Database searches (updated 3 months before submission): MEDLINE (e.g., In-Process, other non-indexed citations), CENTRAL, ClinicalTrials.gov, CTIS, EU Clinical Trials Registry, ICTRP, HTA reports from EEA, Australia, Canada, UK, US, JSC recommendations (if available)	General principles (MEDLINE or Embase, unpublished studies [trial registers], English and German restrictions), PRESS checklist	⊖	No detailed methods; only published literature (no conference abstracts)	No detailed methods; only published literature (no conference abstracts)
		Study design hierarchy should be considered with RCTs with low RoB as the gold-standard design	☑	☑	☑	☑
		Quality assessment of each included study (except for non-randomized controlled trials); Cochrane RoB 2 for RCTs and ROBINS-I for comparative non-randomized studies	☑	CONSORT mentioned/ Annex 1 information	GRADE	⊖
		Studies are included in the networks if relevant for a specific PICO unless indirectly contributing to evidence for a given PICO comparison ("first-order" loops)	⊖	⊖	⊖	⊖
		Evidence networks should be conducted at both "population" and "comparator"-levels (if different)	⊖	⊖	⊖	⊖
Evidence synthesis		**A priori definition of JCA SAP is compulsory**	☑	☑	☑	☑
		Detailed assessment of exchangeability (similarity, homogeneity, consistency [for ITCs]) in each network; when few studies, only similarity can be assessed	☑	Only general principles discussed	Only general principles discussed	Only general principles are discussed
		A priori identification of **effect modifiers** (literature review, expert input, subgroup analyses); thorough justification and reporting of bias direction from missing effect modifiers	☑	☑	⊖	⊖
		Quantitative assessment of **homogeneity** (Q-test, I^2, forest plot inspection) and inconsistency (Bucher method, deviance and DIC statistics, node-splitting) with full reporting of assumptions and reasoning/ decision criteria	☑	⊖	⊖	⊖
		Reporting with full reasoning of conclusion regarding **exchangeability assessments**, pooling of effect estimates across studies and analytical approach selected (including modelling approach, choice of priors, and baseline risk adjustments)	☑	Only general principles discussed	☑	☑
		Comparative effectiveness analyses should pool relative treatment effects between treatments and not absolute effects of a particular treatment arm	☑	Clinical relevance is assessed on a case-by-case basis	Distinction between relative outcomes and continuous outcomes	☑
		When evidence synthesis is feasible for direct comparisons, preference for random-effect models and, in the presence of a connected network, for anchored ITCs (MAIC, STC, ML-NMR) • Population adjustment may not be appropriate when sample sizes are small (difficult to include all relevant effect modifiers)	Detailed guidance (ML-NMR is not included)	Only general principles discussed	⊖	⊖
		When evidence synthesis is needed for indirect comparisons, use MAIC or STC (for two studies of which one has IPD) and IPD NMR if full IPD network is available	Only adjusted ITCs via common comparators and IPD meta-regression accepted	Only general principles discussed	Case-by-case: appropriate justification is needed	Case-by-case: appropriate justification is needed
		When evidence synthesis is not feasible for direct comparisons due to high heterogeneity, use alternative approaches (subgroups splitting [use ICEMAN criteria for credibility assessment], network meta-regression, studies exclusion, PAICs (MAIC, STC, ML-NMR)	Some details (ICEMAN, ML-NMR not included)	Only general principles discussed	Case-by-case: appropriate justification is needed	⊖
		Naive comparisons (i.e., comparisons of absolute outcomes without any adjustment for confounding) should not be used because they do not preserve randomisation	☑	⊖	Disagreement; downgraded within GRADE system	⊖
		Additional topics for consideration; testing against a shifted null hypothesis for unknown or missing confounders, issues with conditional and marginal effect estimates calculation in STC, distribution of weights in MAIC	Partial agreement	⊖	⊖	ITCs very unlikely to be acceptable
		Non-randomized studies (single-arm trials, observational studies) carry a very high risk of confounding bias • Adjustment methods require all effect modifiers and confounders to be measured and pre-specified (to be included in the JCA SAP) • Due to greater uncertainty, larger treatment effect sizes are needed	Only in justified exceptional cases; detailed guidance on analytical methods	Detailed guidance on analytical methods (importance of French data use)	Only in justified exceptional cases; minimal guidance on analytical methods	Detailed guide for RWE protocol development (study design, analytics, QC, transparency and replicability)
		Independently of methods selected, conduct **sensitivity analyses** and report results in full (assumptions, deviations, directionality)	Additional criteria for sample size by subgroup (≥10) and number of events (≥10)	☑	☑	☑
		Validated **surrogate outcomes** can be considered but surrogacy should be demonstrated and clearly reported	Stricter criteria	More relaxed criteria	More relaxed criteria, can be supported by expert opinion	⊖
		Multiplicity statistical hypothesis is not feasible beyond a few primary and secondary analyses; pre-specification and appropriate results reporting is necessary	☑	☑	Covered within GRADE: downgrade for non-specified analyses	⊖
		Full assessment and description of **certainty** of results (internal, external validity and statistical precision) is needed; the certainty of results **is independent of the medical context of the PICO question**	Partial agreement; for extremely rare diseases or very specific disease constellations, the demand for (parallel) comparative studies may be inappropriate	RCT absence can be acceptable based on medical context (unmet need, orphan disease)	Covered within GRADE	☑
		Evidence appraisal systems should not be used; no hierarchy in outcomes assessment	GRADE, inferential statistical thresholds, MCID	MCID	GRADE, MCID	⊖

☑ Agreement ⊖ Not discussed

Abbreviations: CENTRAL, Cochrane Central Registry of Controlled Trials; CHMP, Committee for Medicinal Products for Human Use; CONSORT, CONsolidated Standards Of Reporting Trials; CTIS, Clinical Trials Information System; DIC, deviance information criterion; EEA, European Economic Area; EMA, European Medicines Agency; EU, European Union; G-BA, Germany's Federal Joint Committee; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HTA, health technology assessment; HTAR, health technology assessment regulation; ICEMAN, Instrument for assessing the Credibility of Effect Modification Analyses; ICTRP, International Clinical Trials Registry Platform Search Portal; PD, individual patient data; ITC, indirect treatment comparison; JCA, joint clinical assessment; JSC, joint scientific consultation; MAIC, matching-adjusted indirect comparison; MCID, minimal clinically important difference; ML-NMR, multi-level network meta-analysis; PAIC, population-adjusted indirect comparison; PICO, population, intervention, comparator, outcome; PRESS, Peer Review of Electronic Search Strategies; QC, quality control; RCT, randomized controlled trial; RoB, risk of bias; ROBINS-I, Risk of Bias In Non-randomized Studies-of Interventions; RWE, real-world evidence; SAP, statistical analysis plan; SLR, systematic literature review; STC, simulated treatment comparison; Tx, treatment; UK, United Kingdom; US, United States

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