Uncertainty about how to translate JCA into national HTA submissions (EU-4 and Poland): a systematic comparison from an industry perspective

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Background

- There is uncertainty about incorporating Joint Clinical Assessment (JCA) reports into national submissions.

Objective & Methods

- This analysis examines core JCA evidence requirements and how they differ from national health technology assessment (HTA).
- A targeted review of EU4 and Polish national HTA guidance – supported by searches of HTA websites, stakeholder webinars, press releases, PubMed, and grey literature – was conducted to compare JCA and national methodological requirements across key domains. Where formal guidance was limited, expert judgement was applied.

Results

- The JCA assesses clinical evidence for the broader EU population, whereas national HTAs highly prioritise local relevance.
- In the JCA dossier, manufacturers must justify the representativeness of populations, comparators, and outcomes, but country-specific data are not required.
- For systematic information retrieval, the JCA aligns with international standards, incorporates the Clinical Trials Information System (CTIS), and does not require Embase (supplementary).
- While overall survival (OS) is an established HTA outcome, the JCA focuses on patient-centred outcomes, whereas Germany emphasises patient-relevant benefits.
- Validated surrogates may replace a patient-centred outcome in the JCA only if necessary. JCA considers established minimal important differences (MID) for PROs when available, whereas IQWiG/G-BA use a fixed ≥15% of scale range as the threshold for a clinically relevant change.
- JCA supports fixed (FEM) and random effects models (REM) for meta-analyses. Network meta-analysis (NMA) can be applied even when head-to-head (H2H) studies for the comparison of interest are available.
- There is a general caution in applying population-adjusted methods, primarily due to concerns about multiplicity.

Figure 1. High-level comparison of clinical evidence requirements across selected dossier guidelines (JCA[1-6], G-BA[7]/IQWIG[8], HAS[9], AEMPS[10], AIFA[11], AOTMiT[12])

The JCA dossier takes a broad, cross-national approach that reflects the diversity of Member States' healthcare systems and priorities

Structured but still evolving

Systematic Literature Review (SLR)	Risk of Bias (RoB)	Population & Subpopulations	Comparators	Clinical Outcomes	Patient-Reported Outcomes (PRO)	Surrogates & Composite endpoints	Meta-analysis	Indirect Treatment Comparison (ITC)
▪ MEDLINE, Cochrane ▪ CTs.gov; EU-CTR, CTIS, EMA Clinical Data platform ▪ Patient registries ▪ HTA reports ▪ EMA submission ▪ ≤3 months old ▪ Only full-text studies	▪ RoB 2.0 (for RCTs) ▪ ROBINS-I (for non-RCTs) ▪ QUADAS-2 (for diagnostics)	▪ Defined in PICO scheme during the scoping process ▪ Separate PICO for each subpopulation (based on different comparators, specific tumour entities e.g., tumour types, or differing prognoses with expected differences in effectiveness) ▪ EBM standards	▪ Individualised treatment comparator ▪ A comparison (and thus effect estimates) against each of the treatments required	**Patient-centric, clinically relevant:** ▪ Mortality ▪ Morbidity ▪ HRQoL ▪ Safety	▪ A broad PROs range accepted ▪ No strict preference; validated and fit-for-purpose ▪ VAS: Accepted if justified/validated ▪ Blinding: Not strictly required ▪ Responder/MID: Encouraged; context-dependent	▪ Surrogates: when final outcomes unavailable, strong validation required ▪ Composite endpoints: acceptable if components have comparable importance; disaggregated reporting required	▪ FEM and REM can be used, with REM preferred (as standard approach) ▪ FEM: inverse variance for continuous data and Mantel-Haenszel for binary data ▪ REM: Knapp-Hartung with Paule-Mandel as standard (≥5 studies)	▪ Preferred adjusted/anchored methods ▪ Bucher ITC for a single comparator ▪ NMA with REM (frequentist or Bayesian both applicable) ▪ Population-adjusted ITCs allowed if clearly justified and sensitivity checked

The German G-BA/IQWiG has the most sophisticated and highly specified requirements regarding appropriate comparator therapies and acceptable statistical methods

Most formalised and prescriptive

Systematic Literature Review (SLR)	Risk of Bias (RoB)	Population & Subpopulations	Comparators	Clinical Outcomes	Patient-Reported Outcomes (PRO)	Surrogates & Composite endpoints	Meta-analysis	Indirect Treatment Comparison (ITC)
▪ MEDLINE, Embase^, Cochrane ▪ CTs.gov, EU-CTR, EMA Clinical Data, ICTRP, Arzneimittel-Informationssystem ▪ EMA pivotal studies ▪ G-BA homepage ▪ ≤3 months old ▪ CSRs or published full-texts (abstracts only as supplementary on e.g., most recent data)	▪ RoB 2.0 (for RCTs) ▪ ROBINS-I (for non-RCTs) ▪ QUADAS-2 (for diagnostics)	▪ PICO informed by the SmPC; segmentation influenced by comparator ▪ ≥ 80% SmPC comply with the trial => full population used ▪ < 80% => slicing to patients that comply with SmPC in the subpopulation of interest	▪ Formal, predefined as ACT - the best-established national alternatives supported by robust evidence ▪ H2H by RCT strongly preferred; limited acceptance of ITC; comparison with BSC rarely sufficient unless mandated by G-BA	▪ **Only patient-relevant and validated**: mortality, morbidity, HRQoL, safety (AEs) ▪ OS required (PFS often rejected) ▪ The final outcomes in selected domains prioritised	▪ HRQoL, symptoms, fatigue, pain (strict validation) ▪ EQ-5D, SF-36, EORTC QLQ-C30 ▪ VAS: Explicitly accepted for certain domains (e.g. pain) ▪ Blinding: Strongly preferred ▪ Responder analyses require ≥15% of the scale range; smaller MID-based differences are generally rejected	▪ Surrogates: limited acceptance, unless validated on study level and individual level per specific IQWiG guidance ▪ Composite endpoints rarely accepted; mandatory presentation of components	▪ REM according to Knapp-Hartung method ▪ Paule-Mandel method for heterogeneity estimation	▪ ITCs are rarely accepted by G-BA ▪ If applied, anchored ITC using based on RCTS with adequate bridge comparators recommended (Bucher ITC) ▪ NMAs are rarely accepted

Other European HTA agencies with established frameworks tend to be less stringent on specific requirements and more flexible in their methodological approaches

Less rigid, more pragmatic, greater assessor flexibility

Systematic Literature Review (SLR)*	Risk of Bias (RoB)*	Population & Subpopulations*	Comparators*	Clinical Outcomes*	Patient-Reported Outcomes (PRO)*	Surrogates & Composite endpoints*	Meta-analysis*	Indirect Treatment Comparison (ITC)*
▪ MEDLINE, Cochrane, Embase (required or expected) ▪ CT.gov + EU-CTR (+ other registries) ▪ EMA reports (EPARs) + national HTA ▪ ≤3–6 months old ▪ Full-text peer-reviewed or CSRs required (abstracts only as supplementary on e.g., most recent data)	▪ RoB 2.0 (for RCTs) ▪ ROBINS-I (for non-RCTs) ▪ QUADAS-2 (for diagnostics)	▪ FR: SmPC (reimbursement may target a subgroup, but data must support the full label; only pre-specified groups apply) ▪ SP/IT/PL: PICO may differ from SmPC; (subpopulation are considered when evidence suggests heterogeneity, even if not pre-specified or the comparators differ between the subpopulations)	▪ All anchor the comparator in SoC; clearly refer to the current national, clinical practice ▪ H2H vs chosen comparator preferred; if not feasible, explicitly justified ITC or comparison with BSC acceptable	**Patient-centric, clinically relevant and validated** ▪ OS preferred by all ▪ The final outcomes prioritised by all ▪ A validated link to primary outcomes must be justified ▪ FR: Management of multiplicity (i.e., hierarchical testing of secondary outcomes expected, otherwise exploratory)	▪ Validated instruments are essential ▪ VAS possible as supportive ▪ Blinding preferred, but not absolute ▪ Responder/MID usable if robustly justified	▪ Surrogates: accepted if strongly validated and linked to patient-relevant; otherwise downgraded or rejected ▪ Composite endpoints: Accepted only if all components are meaningful and shown separately	▪ FEM and REM accepted, if justified ▪ FEM: Typically, inverse variance (continuous) or Mantel–Haenszel (binary) ▪ REM: considered robust methods and best practice and are likely acceptable if used	▪ ITCs/NMAs accepted, if H2H unavailable (similarity, homogeneity, consistency check) ▪ Adjusted/anchored ITCs (e.g., Bucher) and NMAs recognized ▪ Unanchored ITCs (e.g., MAIC/STC) considered only in rare cases (with high caution)

^The relevance of the Embase database is currently under evaluation by IQWIG and may not be required in future assessments [13]; *Unless otherwise noted, comments refer to the selected sample: France, Spain, Italy, and Poland.

Conclusions

- EU HTA agencies adhere to a recognised methodological framework comprising systematic evidence retrieval, critical quality appraisal, and evidence synthesis (quantitative where feasible), with variability across agencies in the depth and application of these steps.
- When the HTA research question (PICO) is aligned, major divergences in required clinical evidence between the JCA and national dossiers are unlikely. Only slight methodological differences – such as analysis preferences or data presentation formats – are expected to remain.
- Effective investment in the JCA process could meet the vast majority of requirements across Member States. Nevertheless, national HTA bodies will continue to require context-specific submissions. Early and collaborative engagement between agencies and manufacturers remains essential.

References

1. EMA. Methodological guideline for quantitative evidence synthesis: direct and indirect comparisons (Adopted on 8 March 2024); **2.** EMA. Practical guideline for quantitative evidence synthesis: direct and indirect comparisons (Adopted on 8 March 2024); **3.** EMA. Guidance on outcomes for joint clinical assessments (Adopted on 10 June 2024); **4.** EMA. Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in joint clinical assessments (Adopted on 10 June 2024); **5.** EMA. Guidance on validity of clinical studies (Adopted on 04 July 2024); **6.** EMA. Guidance on filling in the joint clinical assessment (JCA) dossier template – Medicinal products (Adopted on 08 October 2024); **7.** G-BA. https://www.g-ba.de/; **8.** IQWiG. https://www.iqwig.de/ueber-uns/methoden/methodenpapier/; **9.** HAS. https://www.has-sante.fr/jcms/c_2035649/en/assessment-of-medicinal-products; **10.** AEMPS https://www.aemps.gob.es/medicamentos-de-uso-humano/informes-de-posicionamiento-terapeutico/; **11**. AIFA. https://www.aifa.gov.it/en/domande-e-risposte-per-le-aziende; **12.** AOTMiT. https://www.aotm.gov.pl/wytyczne-oceny-technologii-medycznych/; **13**. IQWIG. [GA24-04] . https://www.iqwig.de/en/projects/ga24-04.html

Abbreviations: ACT, Appropriate Comparator Therapy; AE, adverse event; AEMPS, La Agencia Española de Medicamentos y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; AOTMiT, Agency for Health Technology Assessment and Tariff System; BSC, Best Supportive Care; CT, Clinical Trial; CTIS, Clinical Trials Information System; EBM, Evidence-Based Medicine; EMA, European Medicines Agency; EMBASE, Excerpta Medica Database; EPAR, European Public Assessment Report; EORTC, European Organisation for Research and Treatment of Cancer; EQ, EuroQol (generic HRQoL instrument, e.g. EQ-5D); EU, European Union; EU-CTR, EU Clinical Trials Register; FEM, Fixed Effects Model; FR, France; H2H, head-to-head; HAS, Haute Autorité de Santé; HTA, Health Technology Assessment; ICTRP, International Clinical Trials Registry Platform (WHO); IT, Italy; ITC, Indirect Treatment Comparison; IQWIG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; JCA, Joint Clinical Assessment; MAIC, Matching-Adjusted Indirect Comparison; MEDLINE, Medical Literature Analysis and Retrieval System Online; MID, Minimal Important Difference; NMA, Network Meta-Analysis; OS, Overall Survival; PFS, Progression-Free Survival; PICO, Population, Intervention, Comparator, Outcome; PL, Poland; PRO, Patient-Reported Outcome; QLQ, Quality of Life Questionnaire; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; RCT, Randomised Controlled Trial; REM, Random Effects Model; ROBINS, Risk Of Bias In Non-randomised Studies; SF, Short Form Health Survey (e.g. SF-36); SLR, Systematic Literature Review; SmPC, Summary of Product Characteristics; SoC, Standard of Care; SP, Spain; STC, Simulated Treatment Comparison; VAS, Visual Analogue Scale

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