Mapping a Path to Standardized Evidence Quality Tools across EU HTA Agencies and NICE. Is EU Joint Clinical Assessment Guidance Falling Behind?

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Lack of standardisation across health technology assessment (HTA) guidance on quality tools for study designs other than randomised controlled trials (RCTs) may affect the evidence submitted as part of European Union (EU) Joint Clinical Assessments (JCA) and consistency in decision-making informed by such evidence.

Background

- HTAs are a crucial process in healthcare decision-making, with the aim to establish the added benefit of a novel therapy over the existing standard of care.
- HTA methods and processes, however, differ across countries potentially leading to different decisions being made.
- In the EU, the introduction of the JCA aims to substitute the parallel clinical evaluations by multiple country-specific HTA bodies. This single, streamlined, harmonised clinical relative effectiveness assessment, will also support member states that do not necessarily have the capacity to undertake their own assessments to inform local decision-making.
- Evidence quality is considered a key driver in building trust in the interpretation of results and impact on final decision-making. For that reason, use of established tools for recording data quality assessment is considered standard practice in evidence presentation and synthesis.
- However, the decision-making criteria for the process of evidence quality assessment are not consistently reported.

Objective

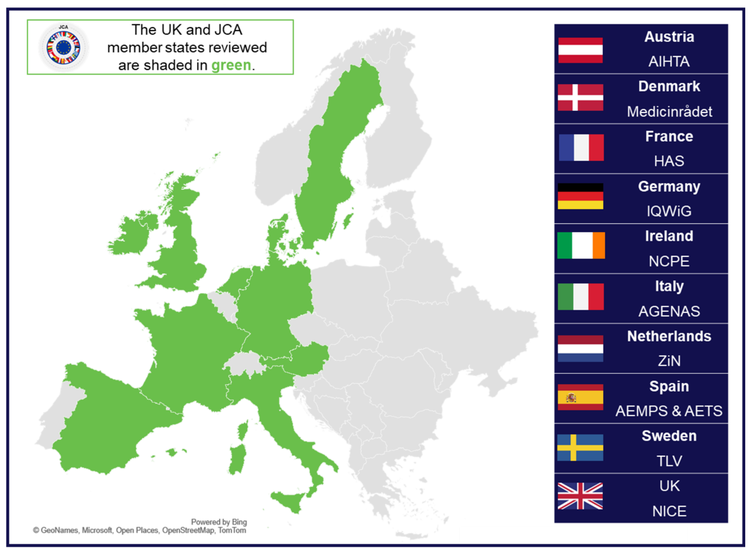
- This study aimed to identify and present current guidance on the conduct of study/data quality (risk of bias [RoB]) assessment to support HTAs across core EU HTA agencies, the upcoming JCA and the National Institute for Health and Care Excellence (NICE).

Methods

- A pragmatic review was conducted in June 2023 of HTA guidance documents across several core European HTA agencies, EUnetHTA 21 (responsible for coordinating and implementing JCA guidance until September 2023) and the European Commission (establishing the Regulation on health technology assessment [HTAR] which sets the legal framework for the upcoming EU JCA), and NICE (Figure 1). Although not part of the EU JCA, the latter agency was included in the review due to its detailed methods manual and global role in setting methodological standards.

Methods (cont.)

Figure 1. Overview of HTA organisations reviewed



Abbreviations: (see below)

- The website of each agency/organisation was searched for guidance or information on data quality assessment (RoB) criteria and recommended assessment tools. The review findings were extracted by two reviewers into a pre-defined extraction grid and qualitatively synthesised by study design and HTA jurisdiction.

Results

- Of the 13 agencies and organisations (representing 10 countries and the EU JCA) reviewed, 11 provided relevant guidance on data quality assessment (Table 1). No information was available from the two Spanish agencies AEMPS and AETS.
- The detail of guidance on data quality assessment varied across agencies. Where specific RoB tools were recommended, this was generally divided by study design, such as RCTs, and observational/real-world evidence (RWE) studies.
- Five national HTA bodies (AIHTA, HAS, IQWiG, NICE, TLV) recommended specific assessment tools for RCTs, all of which included the Cochrane RoB 2 tool. NICE also recommended the EPOC RoB tool and the CASP RCT checklist as alternatives. Medicinrådet and ZiN referred to the GRADE framework for the overall quality assessment.

Results (cont.)

- Six national HTA bodies (AGENAS, AIHTA, HAS, IQWiG, NICE, TLV) recommended specific RoB tools for RWE studies, although the agencies differed in the type of tool recommended. The ROBINS-I and QUADAS-2 tools were most commonly cited for observational studies (n=3) and diagnostic accuracy studies (n=3), respectively. Other tools included the Newcastle-Ottawa Scale (non-randomised studies) and PROBAST (prognostic studies). The remaining three HTA agencies (Medicinrådet, NCPE, ZiN) highlighted that quality assessment should be carried out using appropriate and/or validated tools without recommending specific RoB tools.
- The legal framework establishing the EU JCA (HTAR by the European Commission) does not include specific provisions for a study quality assessment other than a reference to the need for the strengths and limitations of the evidence to be presented. Recent methods guides and the JCA dossier template developed by EUnetHTA 21 are mainly based on 2015 guidance established under a prior EU funding agreement; the Cochrane RoB tools and ROBINS-I tool are recommended for RCT and observational evidence, respectively. The guidance does not require a quality assessment of single-arm trials, cross-sectional studies or case reports/series given their limited value for relative effectiveness analysis.

Conclusions

- Current study quality assessment processes and guidance around informing HTA submissions vary across Europe which can “result in [manufacturers] being confronted with multiple and divergent requests for data [and] lead to both duplication and variation in outcomes.” (HTAR)
- Cochrane RoB 2 tool was recommended by all organizations for assessing quality of evidence from RCTs. However, variability exists for recommendations for quality assessment of data from other study designs.
- With the end of the EUnetHTA 21 funding programme and limited information available on which organisation will drive the JCA methods development going forward, it is unclear whether differences in recommended tools across HTA agencies will result in inconsistencies in data assessment and its impact on final decision-making.

Table 1. Recommended data quality assessment tools by study design and country

	EUnetHTA – JCA[1,2]	Austria AIHTA[3]	Denmark Medicinrådet[4]	France HAS[5]	Germany IQWiG[6]	Ireland NCPE[7]	Italy AGENAS[8]	Netherlands ZiN[9]	Spain AEMPS[10] & AETS[11]	Sweden TLV[12]	UK NICE[13]
RCT	Cochrane RoB 2	Cochrane RoB	GRADE	Cochrane RoB 2	Cochrane RoB 2	None	None	GRADE	None	Cochrane RoB 2	Cochrane RoB 2 EPOC CASP RCT checklist
RWE	ROBINS-I RoBANS	Deeks et al., 2003	None	Cochrane (diagnostic) QUADAS 2 (diag. accur.)	ROBINS-I QUADAS 2 (diag. accur.) PROBAST (prognostic)	None	Newcastle-Ottawa scale	GRADE	None	ROBINS-I QUADAS-2 (diag. accur.) CASP (qualitative)	ROBINS-I EPOC CASP RCT checklist Newcastle-Ottawa scale QUIPS

Abbreviations: AEMPS, Spanish Agency of Medicines and Medical Devices; AETS, Evaluación de Tecnologías Sanitarias; AGENAS, Italian National Agency for Regional Healthcare Services; AIHTA, Austrian Institute for Health Technology Assessment; CASP, Critical appraisal skills programme; EPOC, Effective Practice and Organisation of Care; EUnetHTA, European Network for Health Technology Assessment; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HAS, Haute Autorité de santé; HTAR, Regulation (EU) 2021/2282 on health technology assessment; IQWiG, Institute for Quality and Efficiency in Health Care; JCA, Joint Clinical Assessment; NCPE, National Centre for Pharmacoeconomics; NICE, National Institute for Health and Care Excellence; NRS, Numeric Rating Scale; PROBAST, Prediction model Risk Of Bias ASsessment Tool; RCT, randomised controlled trial; RoB, risk of bias; RoBANS, Risk of Bias Assessment tool for Non-randomized Studies; TLV, The Dental and Pharmaceutical Benefits Agency; UK, United Kingdom; ZIN, National Health Care Institute (Zorginstituut Nederland)

References

1. https://health.ec.europa.eu/health-technology-assessment/regulation-health-technology-assessment_en; 2. https://www.eunethta.eu/d4-6/; 3. https://aihta.at/page/methoden/en; 4. https://medicinraadet.dk/om-os; 5. https://www.has-sante.fr/jcms/r_1499251/en/choices-in-methods-for-economic-evaluation; 6; https://www.iqwig.de/en/about-us/methods/methods-paper/; 7. https://www.ncpe.ie/submission-process/hta-guidelines/; 8. https://www.agenas.gov.it/aree-tematiche/monitoraggio-e-valutazione/lea; 9. https://www.zorginstituutnederland.nl/publicaties/publicatie/2023/04/11/beoordeling-swp-2023; 10. https://www.aemps.gob.es/medicamentos-de-uso-humano/investigacion_medicamentos/; 11. https://www.isciii.es/QuienesSomos/CentrosPropios/AETS/Paginas/Servicios.aspx; 12. https://www.tlv.se/in-english/medicines/apply-for-reimbursement/the-decision-process.html; 13. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.

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