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Guidance for real-world evidence generation for the Joint Clinical Assessment process and its implications for country-specific HTA body acceptability

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Background and Objectives

- Real-world evidence (RWE) is increasingly used to support decision-making in health technology assessments (HTA).
- With the implementation of the Joint Clinical Assessment (JCA) under the EU HTA Regulation in January 2025, health technology developers (HTDs) must consider JCA and country-specific HTA body requirements for designing transferable RWE studies.
- RWE studies may be necessary for JCA to characterise treatment patterns and comparative effectiveness, especially for HTDs with single-arm trial evidence.

This study aims to assess the feasibility of conducting transferable RWE studies that could be acceptable for JCA and select European HTA bodies.

Methods

We reviewed guidance from the EU HTA Coordination Group (CG)[1,2], the French Haute Autorité de Santé (HAS)[3], the German Institüt für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)[4], the UK's National Institute for Health and Care Excellence (NICE)[5] and related reports[6-7] to compare RWE study requirements.

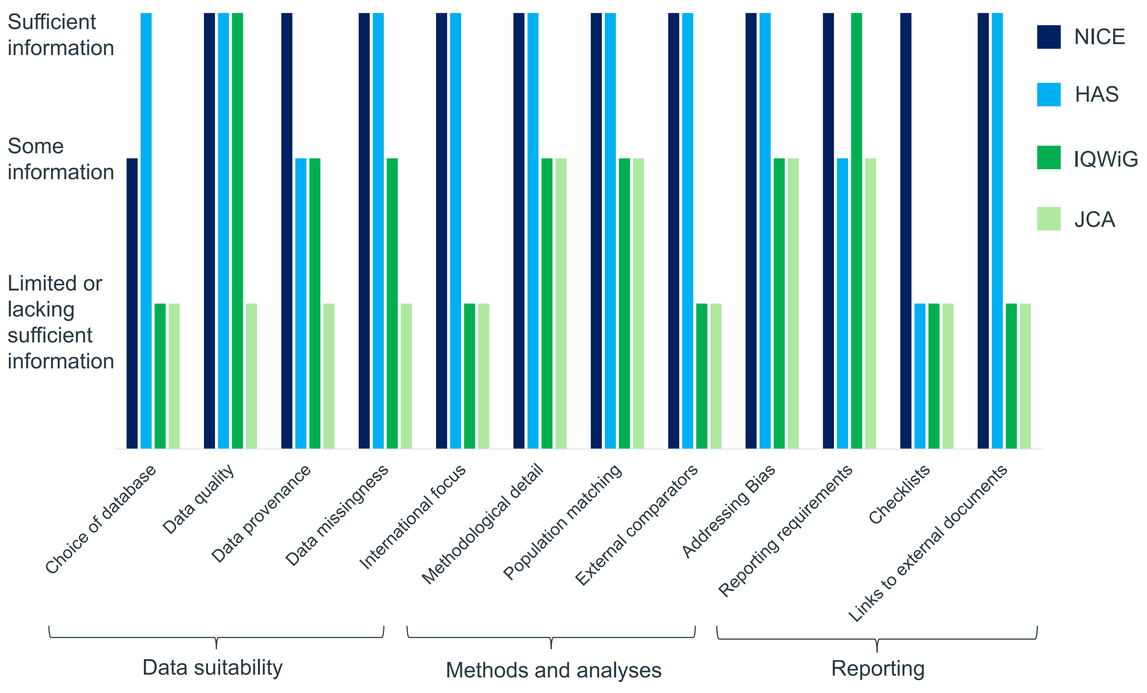
We structured available information for RWE study requirements under three main categories: **data suitability**, **methods and analyses** and **reporting (Figure 1)**. Additional information was extracted for statistical analysis methods to address **confounding**, **information** or **selection bias** (**Table 1**). For each extracted item, we qualitatively assessed whether the guidance provided: a) sufficient information; b) some information; c) limited or lacking sufficient information.

Results

Our review reveals a heterogeneous picture for general RWE study requirements, with agencies differing in topics and extent of information provided (**Figure 1**).

- There is a lack of clear guidance outlining RWE study requirements for JCA. The EU HTA CG guidance for direct and indirect treatment comparisons (ITCs)[1,2] includes only limited considerations for the analysis of non-randomised evidence.
- IQWiG's general methods[4] justify the use of non-randomised evidence in exceptional cases. For the latter, some information for appropriate data collection and analysis methods is provided in IQWiG's rapid report for routine practice data[5].
- HAS[3] and NICE[5] have developed dedicated RWE frameworks. Both frameworks provide sufficient information across most items related to data suitability and methodological guidance. NICE clearly outlines reporting requirements and checklists as well as links to resources for assessing data suitability, such as the Data Suitability Assessment Tool (DataSAT). The NICE framework also addresses RWE studies involving external comparisons, while HAS discusses considerations for these studies in a subsequent position paper[7].

Figure 1. Depth of coverage of topics related to study planning, data suitability, analysis methods, and results reporting across the HTA bodies included in the review



Our findings on statistical analysis methods to mitigate bias in comparative RWE studies (**Table 1**) further identified a lack of sufficient RWE guidance for JCA compared to the country-specific HTA bodies.

- JCA ITC guidance briefly covers unanchored comparisons using non-randomised patient-level data, including propensity score approaches to adjust for observed confounding. Methods to address unobserved and time-varying confounding are briefly mentioned, while insufficient detail is provided on handling information and selection bias.

Table 1. Overview of analysis methods to mitigate confounding bias associated with comparative RWE studies

Type of bias	Source of bias	Analysis method to minimise bias	Method coverage in relevant guidance			
			NICE	HAS	IQWiG	JCA
Confounding bias	Observed confounding	Propensity score stratification	●	●	●	●
		Propensity score matching	●	●	●	●
		Multiple/Multivariable regression	●	●	●	●
		Inverse probability of treatment weighting (IPTW)	●	●	●	●
	Unobserved confounding	Instrument-based methods (or quasi – experimental methods)	●	●	●	●
		Sensitivity analysis	●	●	●	●
	Time-varying confounders	G-methods (including marginal structural models with weighting)	●	●	●	●
	Residual confounding	Negative controls	●	●	●	●
		Informed by external data on confounder-outcome relationship	●	●	●	●
Information bias	Informative censoring	G-methods (including marginal structural models with weighting)	●	●	●	●
	Handling missing data	Complete record analysis	●	●	●	●
		Imputation	●	●	●	●
		Inverse probability weighting	●	●	●	●
		Maximum likelihood estimation	●	●	●	●
		Sensitivity analysis	●	●	●	●
	Measurement error	Calibration and advanced methods	●	●	●	●
Selection bias	Patient inclusion	Consecutive inclusion of patients	●	●	●	●
		Sensitivity analysis	●	●	●	●

● Sufficient information ● Some information ● Limited or lacking sufficient information

- HAS, IQWiG and NICE advocate for using target trial emulation as the gold-standard approach for designing comparative RWE studies.
- NICE most clearly details statistical approaches for comparative RWE studies and methods to minimise bias across HTA bodies.
- The HAS framework provides sufficient information for methods to address selection bias, but includes fewer details than NICE to mitigate confounding. HAS also covers less methods than NICE to address information bias.
- IQWiG's rapid report focuses on methods to address observed and unobserved confounding and mentions sensitivity analyses to address missing data.
- These findings were consistent with perspectives from broader multi-stakeholder initiatives, like the RWE4Decisions and the GetReal Institute.

Conclusions and recommendations

- In the absence of formal JCA RWE guidance, HTDs should recognize that the utility and acceptance of RWE studies in the context of JCA remains unclear.
- Until JCA RWE standards are formalised, HTDs should base the design of methodologically robust RWE studies on country-specific guidance. Even though the most comprehensive RWE framework available is from a non-EU HTA body (NICE), it provides internationally relevant methodological standards.
- HTDs should also account for the aspect of transferability of RWE studies across EU member states and consider methodological overlap within country-specific guidance. Importantly, HTDs should assess whether the data sources are sufficiently generalizable, as national differences in data relevance may still limit transferability.
- **A clear JCA RWE framework is therefore necessary to harmonise transferability and outline expectations for study acceptability across European HTA bodies. In the meantime, HTDs should monitor developments in the guidance and prepare to adapt their RWE strategies as official expectations become clearer.**

References

1. Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. Adopted on 8 March 2024.
2. Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. Adopted 8 March 2024.
3. HAS. Real-world studies for the assessment of medicinal products and medical devices, June 2021.
4. IQWiG General Methods Version 8.0. 25 February 2025.
5. NICE. NICE real-world evidence framework. September 2025.
6. IQWiG. Concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a social code book V (SGB V) (10 January 2020)
7. Vanier A, et al. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. BMJ Evidence-Based Medicine. 2024;29(1):1

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