EVIDENCE EXPECTATIONS VS. EVIDENTIARY REALITY: LESSONS FROM MISSING INFORMATION NOTICES IN ONCOLOGY JOINT CLINICAL ASSESSMENTS

HTA115

CONCLUSIONS

The extent and recurring nature of the information gaps identified in the MINs for catequentinib dihydrochloride, autologous melanoma-derived TIL, and sintilimab reflect the high evidence expectations for JCAs, even in a rare oncology setting, such as sarcoma, where evidence bases are inherently limited. The requirement to satisfy these standards under tight timelines represents a substantial operational and resource burden for developers, particularly where comparative evidence is limited. To avoid additional JCA terminations in future, there is a need for early evidence generation and contingency planning by developers, meaningful dialogue between developers and JCA assessors, and a pragmatic JCA framework that acknowledges evidentiary constraints, especially in rare diseases.

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INTRODUCTION

- Since 12 January 2025, new oncology active substances and advanced therapy medicinal products (ATMPs) have been subject to Joint Clinical Assessment (JCA) under Regulation (EU) 2021/2282.[1]
- Article 9 requires a complete, transparent, appropriately analysed and fully documented dossier for every population, intervention, comparator and outcome (PICO) identified within the JCA scope; under Article 10, any gaps trigger a Missing Information Notice (MIN) and, if unresolved, discontinuation of the assessment.
- Early JCAs have highlighted these strict documentation standards and the challenges with meeting the requirements, especially associated with limited evidence availability.[2] As the only public record of what assessors judged missing before assessment, MINs offer direct, structured insights into where dossiers fall short of JCA expectations and offer potential learnings for manufacturers for future JCAs.

STUDY OBJECTIVE & METHODOLOGY

- To evaluate the evidence requirements imposed under the JCA and assess their feasibility for oncology therapies, using MINs as a structured data source.
- We conducted a qualitative analysis of the three publicly available MINs issued by the European Commission by October 2026, including only JCAs discontinued because of an incomplete dossier: catequentinib dihydrochloride (synovial sarcoma and leiomyosarcoma; May 2026), autologous melanoma-derived tumor infiltrating lymphocytes (TIL; advanced melanoma; February 2026) and sintilimab (non-squamous, non-small cell lung cancer; September 2026).[3-5]
- Information gaps were categorised by article of Regulation (EU) 2021/2282 and classified into four predefined categories, based on the issues identified: information retrieval, methodological deviations and indirect comparisons, results presentation, and underlying documentation.

RESULTS

- All three MINs were issued following requests for additional information from the European Commission, meaning that developers had made one round of remediation before the notices were issued, as missing information persisted.[3-5]
- Gaps spanned all four categories in each MIN (Table 1), with six key themes identified, with issues associated with:

R Information retrieval

Incomplete systematic evidence retrieval across data sources.

M Methodological deviations and indirect comparisons

Insufficient methodological justification for deviations from Health Technology Assessment Coordination Group (HTACG) guidance.

Incomplete certainty-of-evidence assessments.

P Results presentation

Absent or inadequate comparative effectiveness and safety data across PICOs.

Non-compliance with dossier template structure.

D Underlying documentation

Absence of underlying documentation including search strategies, statistical analysis plans, and programming code.

- Collectively, the MINs flagged non-adherence to Articles 9(2), 9(3)(a–d) and 9(4), with most Article 9(4) findings cross-referencing earlier gaps, reflecting the breadth, complexity and overlapping nature of JCA requirements.

Table 1. Information gaps identified in MINs for discontinued JCAs

Requirement	Catequentinib dihydrochloride[3] *Synovial sarcoma and leiomyosarcoma*	TIL[4] *Advanced melanoma*	Sintilimab[5] *Non-small cell lung cancer*
Art. 9(2) *Complete and up-to-date evidence for the assessment scope*	**R** Evidence identification and synthesis; non-randomised study search; search reporting; excluded registry studies **M** Inclusion/exclusion justification; ITC feasibility; study selection rationale; certainty of effects in PICO 4. **P** PICO presentation; omitted PICO rationale; scope parameter evidence; study characteristics; HTACG-aligned results.	**R** Information retrieval for PICO 4 and PICO 10-13.	**P** Study characteristics and outcome information; individual study results and Kaplan-Meier censoring.
Art. 9(3)(a) *Complete with regard to the available studies*	*Cross-reference to Art. 9(2)* **R** Evidence identification; selection process and study exclusions; search limits; HTA agency website search; patient registry search.	*Not cited*	*Cross-reference to Art. 9(2)* **R** Results for each information source; ClinicalTrials.gov search; HTA agency website search. **D** ClinicalTrials.gov RIS files and search strategies.
Art. 9(3)(b) *Appropriate methods*	**M** Methods used to answer research questions; ITC feasibility and study exclusions; methods according to the dossier template and HTACG guidance; SLR and study selection approach; sensitivity analysis methods.	**M** Methods for PICOs 1, 2 and 6; justification of the absence of sensitivity analyses; analysis methods for included studies. **D** External comparison certainty evidence; sensitivity analysis documentation.	**M** Exchangeability of studies in indirect comparisons.
Art. 9(3)(c) *Structured, transparent presentation*	**P** Template-aligned results; HTACG-aligned results; omitted results sections; relative effectiveness and safety data for PICOs. **R** Information retrieval results.	**D** Manufacturing comparability documentation. **P** Relative effect results for PICOs 1, 2 and 6; EMA-based results for PICOs 5 and 6.	**P** Well-structured, transparent and consistent data presentation.
Art. 9(3)(d) *Underlying documentation*	**D** Underlying documentation presentation; full-text screening and study exclusion justification.	**R** PICO-specific intervention search strategies; third-party study search. **D** Registry search strategy documentation; external comparison certainty evidence.	*Cross-reference to Art. 9(3)(a)*
Art. 9(4) *Annex I content*	*Cross-references to Art. 9(2)–9(3)(d)*	*Cross-references to Art. 9(3)(a)–(d)* **R** Excluded studies and exclusion reasons. **P** Effect measures with 95% CIs and p-values for PICOs 1, 2, 6. **M** RoB signalling question justification; indirect comparison methods and results for PICO 1. **D** External comparison programming code.	*Cross-references to Art. 9(2), 9(3)(a) and 9(3)(b)*

Abbreviations: Art.: Article; CI: Confidence Interval; EMA: European Medicines Agency; EU: European Union; HTA: Health Technology Assessment; ITC: Indirect Treatment Comparison; RIS: Research Information Systems; RoB: Risk of Bias; SLR: Systematic Literature Review.