HTA187

PICO Divergence and Evidence Feasibility in EU Joint Clinical Assessments: Insights from Published Scoping Exercises and the First Tovorafenib Assessment

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Background

- EU Joint Clinical Assessments (JCAs) were introduced in January 2025 under Regulation (EU) 2021/2282 establishing an EU-level approach to the clinical assessment of selected health technologies.
- Population, Intervention, Comparator, and Outcomes (PICO) frameworks are central to the JCA process as they determine the evidence requirements and guide the clinical evaluations.
- While intended to support a harmonized evidence assessment, differences in Member State perspectives and clinical practice may result in multiple PICO configurations for the same health technology.
- PICO divergence can have important implications for evidence feasibility, potentially requiring manufacturers to generate or identify evidence across different populations, comparators, and outcomes.
- Understanding the extent and nature of this divergence, and whether the resulting evidence requirements can be addressed using available evidence, is therefore critical for JCA evidence planning and submission readiness.

Objective

- To characterize the drivers of PICO divergence within the EU JCA framework and understand how divergence may affect evidence feasibility using findings from published PICO scoping exercises and the first published JCA (tovorafenib).

Methods

Targeted literature review

- A targeted literature review was conducted by searching PubMed on June 10, 2026.
- Searches were supplemented with relevant EU HTA guidance and publicly available JCA assessment reports.

Sources of evidence

- EU HTA guidance
- Peer-reviewed publications
- Publicly available JCA analyses

Data Extraction

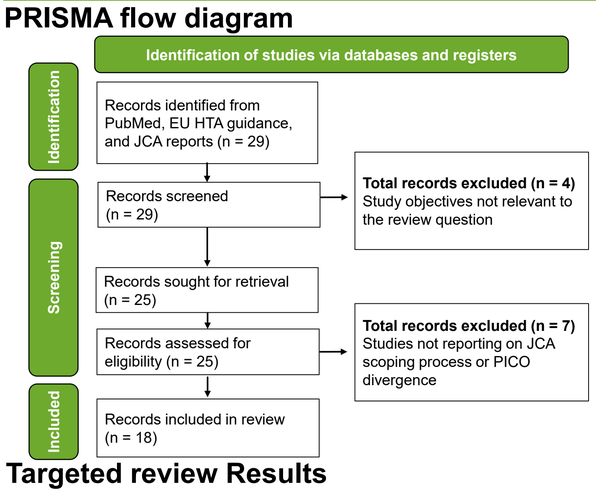
- Therapeutic area and publication type
- Number of participating Member States
- Number of national and consolidated PICOs
- Reported sources of PICO divergence
- PICO domains i.e., Population, Intervention, Comparator, Outcomes contributing to divergence
- Reported implications for evidence generation and feasibility

Data Synthesis

- Information was synthesized descriptively to:
  - identify recurring drivers of divergence
  - characterize the magnitude of PICO variation
  - understand implications for evidence generation
- Findings were supplemented with a case study assessment of the first published medicinal-product JCA (tovorafenib).

Results

PRISMA flow diagram



Targeted review Results

Of the 18 records,

- Six were methodological analyses of JCA implementation
- Five published PICO scoping exercises
- Three simulated JCA assessments
- One real-world JCA evaluation
- Three guidance/methods papers

Key Driver and Magnitude of Divergence[2,4]

Variability was observed across all PICO domains. Differences in comparator requirements across Member States were identified as a major contributor to PICO divergence and increased analytical complexity.

Divergence in comparator selection reflected differences in national standards of care, treatment availability, reimbursement pathways, treatment positioning, and clinical practice patterns.

Population variation was commonly associated with disease severity, biomarker status, treatment line, and eligibility criteria, whereas intervention and outcome requirements were generally more consistent.

These findings indicate that consolidation may reduce, but does not necessarily eliminate, comparator-related variation in evidence requirements.

Results

Results from PICO Scoping Exercises and Simulated JCA Assessments

- Published PICO scoping exercises and simulation studies consistently identified comparator selection as the primary driver of PICO divergence, reflecting differences in national standards of care, treatment availability, reimbursement pathways, and treatment positioning.
- Across 35 reported PICO scoping exercises spanning 20 indications, a mean of approximately 8 consolidated PICOs across 7 participating countries was generated following the JCA scoping process, indicating that clinically meaningful differences in evidence expectations may persist despite consolidation of Member State requirements.[2]
- Population-related variation was most commonly associated with differences in disease severity, biomarker status, treatment line, prior treatment exposure, and eligibility criteria, whereas intervention and outcome requirements were generally more consistent across countries.
- Simulation studies demonstrated the potential upper range of PICO divergence that may be encountered during JCA evidence planning. In one oncology-focused simulation, 67 distinct national PICOs were generated across 25 countries before consolidation, illustrating the substantial variability that can arise when country-specific evidence requirements are considered simultaneously.
- Collectively, these findings indicate that successful PICO consolidation does not necessarily eliminate evidence-generation challenges, as country-specific comparator expectations may continue to create gaps between requested and available comparative evidence.

Evidence Feasibility Assessment using Tovorafenib Case[7]

To determine whether the divergence patterns reported in published literature translate into practical evidence challenges, findings were evaluated against the first published medicinal-product JCA (tovorafenib)

- The JCA for tovorafenib was published on 9 June 2026 following HTACG endorsement on 30 April 2026 and completion of the European Commission procedural review on 19 May 2026.
- Eight PICOs were scoped across three patient populations; however, comparative evidence informed only one final assessment **(Table 1)**.
- Six PICOs could not be addressed because no comparator evidence was available.
- Comparative evidence submitted for one PICO was not retained in the final assessment owing to insufficient information.
- Consequently, only 12.5% of scoped PICOs contributed to the final comparative assessment.
- The tovorafenib experience demonstrates that completion of PICO scoping does not necessarily ensure that each scoped comparison is evidence-feasible.
- Even after PICO consolidation, comparator-specific evidence requirements may remain unsupported by available comparative evidence.

Table 1: PICOs requested/retained in the tovorafenib submission

PICO	Population	Comparator	Comparative-evidence disposition	Reason
PICO 1	Full claimed indication	Individualised: Vinblastine; carboplatin/vincristine; TPCV; dabrafenib/trametinib; everolimus; bevacizumab/chemotherapy	✕	No comparator data available
PICO 2	Full claimed indication	Individualised: Vinblastine; carboplatin/vincristine; TPCV; dabrafenib/trametinib	✕	No comparator data available
PICO 3	Full claimed indication	Carboplatin + vincristine	✕	No comparator data available
PICO 4	Full claimed indication	Vinblastine	✕	No comparator data available
PICO 5	BRAF V600E mutation; age >1 year	Dabrafenib + trametinib	**YES**	—
PICO 6	BRAF V600E mutation; age >1 year	Individualised treatment: Vinblastine; carboplatin + vincristine	✕	No comparator data available
PICO 7	BRAF fusion/rearrangement or V600 non-E mutation	Trametinib	**Submitted, but excluded from the final JCA report**	Unanchored MAIC excluded from the JCA report because TRAM-01 information was insufficient
PICO 8	BRAF fusion/rearrangement or V600 non-E mutation	Individualised treatment: Vinblastine; carboplatin + vincristine	✕	No comparator data available

8 → 1

EVIDENCE-FEASIBILITY

Comparative evidence included for 1 of 8 scoped PICOs.

1 evidence-supported | **6** no comparator data | **1** insufficient information

Discussion

Implications for Manufacturers

Published evidence and early JCA experience suggest that comparator assessment should be considered an evidence-feasibility exercise rather than solely a scoping exercise.

Manufacturers should:

- evaluate potential comparator availability before final PICO scoping
- assess whether comparative evidence can realistically be generated or identified for each anticipated comparator
- identify evidence gaps early enough to support supplementary analyses or evidence-generation activities
- consider evidence-feasibility assessments alongside regulatory and market-access planning

Conclusions

- Early JCA experience and published PICO scoping exercises indicate that comparator heterogeneity is a key driver of PICO divergence and evidence-generation burden.
- The first published JCA (tovorafenib) demonstrates limited comparative evidence coverage in the final assessment. However, as a single-case experience, it cannot establish that PICO divergence caused the observed evidence gap, which may also reflect the indication and underlying study designs.
- Early assessment of comparator availability and evidence feasibility may be critical to ensuring that retained PICOs can be supported by comparative evidence at the time of submission.

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