Best Practices in Oncology Joint Clinical Assessment (JCA) Submissions Under the EU HTA Regulation

Mojgan Gitimoghaddam, PhD - Associate Director
Gaurang Nazar, PhD - Senior Associate Research Scientist

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1. Introduction

The first oncology Joint Clinical Assessments (JCAs) conducted under the European Union (EU) Health Technology Assessment (HTA) Regulation have demonstrated that JCA is not simply another HTA submission. Sponsors are facing increasingly heterogenous evidence requirements, including multiple population-intervention-comparator-outcome (PICO) frameworks, diverse comparator expectations across Member States, compressed timelines, and increased expectations for methodological transparency. Early oncology JCA reports highlight the need for evidence packages that can address diverse clinical practices while maintaining methodological consistency.[1-4]

The EU HTA Regulation (Regulation (EU) 2021/2282) established a framework for collaborative clinical assessments at the EU level, with the objective of reducing duplication of effort, increasing consistency in clinical evidence evaluations, and supporting evidence-based decision-making by Member States.[3] The regulation became applicable in January 2025 for oncology medicines and advanced therapy medicinal products (ATMPs), making oncology the first major therapeutic area subject to mandatory JCA.[1]

The JCA process differs from both regulatory review and traditional national HTA submissions. While the European Medicines Agency (EMA) evaluates benefit-risk profiles for marketing authorization, the JCA focuses on the comparative clinical effectiveness and safety of a given health technology relative to relevant treatment alternatives across multiple healthcare systems.[1,3] The resulting JCA report is intended to inform national HTA processes, although pricing and reimbursement decisions remain the responsibility of individual Member States. Consequently, sponsors must prepare evidence packages capable of satisfying both regulatory and HTA requirements.

The JCA process comprises a series of coordinated activities involving multiple stakeholders, from assessment scoping through publication of the final report (**Figure 1**). Member States are expected to consider published JCA reports when conducting their local HTA evaluations.[3]

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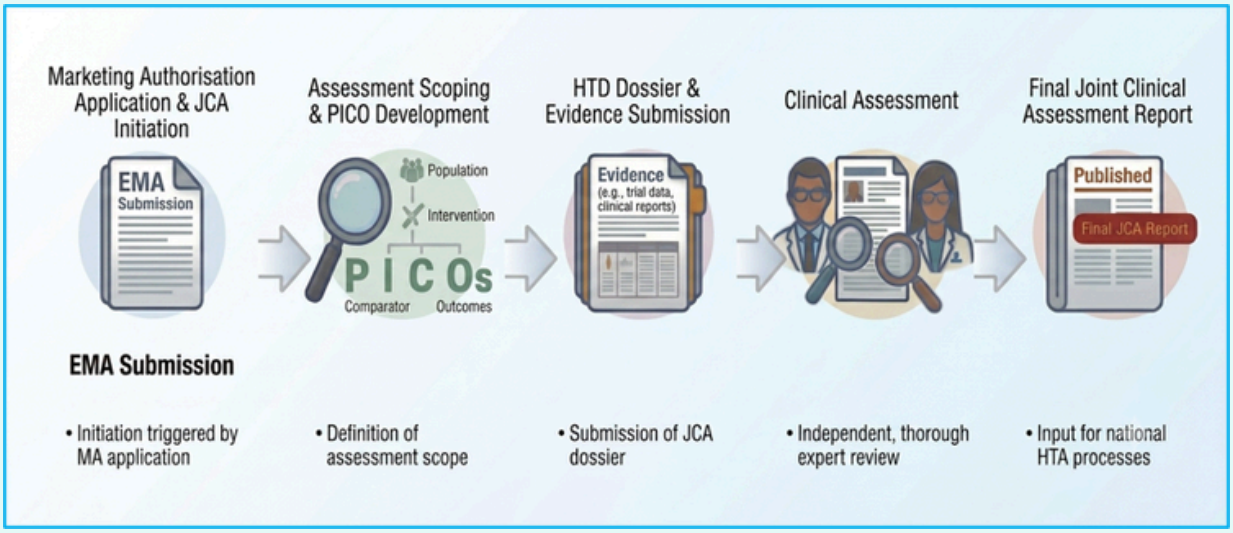

Figure 1. Overview of the EU Joint Clinical Assessment (JCA) Process[1,4]

As additional oncology JCA assessments become available, sponsors will need to adapt evidence-generation strategies, comparator selection approaches, and submission planning processes to meet the requirements of this new framework. This blog reviews key challenges observed in early oncology JCAs and outlines practical best practices that may help sponsors prepare more robust and effective submissions.

Key Takeaways

- Start JCA planning early in clinical development.
- Anticipate multiple PICOs and comparator requirements.
- Establish plan for assessing and reporting overall survival and relevant health-related quality of life measures.
- Ensure methodological transparency and cross-functional alignment.
- Develop integrated evidence packages capable of addressing multiple assessment scenarios.

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2. Emerging Insights from the First Published Oncology JCA Reports

The first published oncology JCA reports provide an opportunity to examine how evidence is being assessed under the new EU HTA framework. In July 2026, the European Commission published JCA reports for lurbinectedin (Zepzelca®)[5] and tarlatamab (Imdyllltra®),[6] both indicated for extensive-stage small cell lung cancer (ES-SCLC). Although approved for the same indication, the two assessments illustrate two very different evidence-generation scenarios. Together, they highlight the importance of aligning evidence packages with anticipated PICO requirements and comparator expectations.

Lurbinectedin (Zepzelca®)

The JCA for lurbinectedin assessed its use in combination with atezolizumab as maintenance treatment for ES-SCLC following first-line induction therapy.[5] The assessment was relatively focused, involving a single population and a single PICO comparing lurbinectedin plus atezolizumab with atezolizumab monotherapy.

The evidence package relied primarily on the phase III IMforte trial, which randomized 483 patients to maintenance treatment with either lurbinectedin plus atezolizumab or atezolizumab alone. The submission provided direct comparative evidence aligned with the requested PICO, eliminating the need for complex indirect comparisons. Outcomes assessed included overall survival (OS), progression-free survival (PFS), response outcomes, health-related quality of life (HRQoL), and safety.

While the availability of direct evidence simplified the assessment, the report[5] still identified important methodological considerations, including the open-label design, unequal follow-up between treatment arms for some patient-reported outcomes (PROs), and potential risks of bias for subjective endpoints.

Key lesson: A well-aligned evidence package supported by direct comparative data can simplify the assessment process, but methodological rigor and transparent reporting remain critical.

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Tarlatamab (Imdyllta®)

The tarlatamab assessment involved a broader and more complex assessment scope.[6] The JCA scope included four patient populations and seven PICOs reflecting differences in treatment-free intervals, platinum sensitivity, and comparator expectations across European healthcare systems.

The phase III DeLLphi-304 study served as the primary evidence source and provided direct comparative data against standard-of-care chemotherapy, including topotecan. However, as not all requested comparators were represented in the trial, the submission incorporated multiple evidence-synthesis approaches, including matching-adjusted indirect comparisons (MAICs), network meta-analyses (NMAs), and indirect treatment comparisons (ITCs) using external studies.

The report[6] highlights the complexity of evaluating treatment effects across multiple comparators and patient populations while ensuring the validity of assumptions underpinning indirect comparisons. It also illustrates how differing standards of care across Member States can substantially broaden JCA evidence requirements.

Key lesson: When direct comparative evidence is unavailable for all anticipated PICOs, robust and transparent evidence-synthesis methods become essential.

Table 1. Emerging Lessons from Early Oncology JCA Submissions

Feature	Lurbinectedin	Tarlatamab
Assessment scope	1 population, 1 PICO	4 populations, 7 PICOs
Primary evidence source	IMforte Phase III RCT	DeLLphi-304 Phase III RCT
Direct evidence	Yes	Partial
Indirect evidence	Not a major component	MAICs, NMAs, and ITCs
Main challenge	Risk of bias and outcome interpretation	Comparator coverage and evidence synthesis
Key lesson	Strong direct evidence simplifies assessment	Broad PICOs require broader evidence strategies

ITC: Indirect Treatment Comparison; MAIC: Matching-Adjusted Indirect Comparison; NMA: Network Meta-Analysis; PICO: Population, Intervention, Comparator, Outcome; RCT: Randomized Controlled Trial.

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Emerging Insights

The first published oncology JCAs illustrate how assessment complexity can differ substantially depending on the breadth of requested PICOs, comparator requirements, and availability of direct comparative evidence. These early assessments highlight several recurring themes that are likely to influence future oncology submissions, including the management of multiple PICOs, evidence-synthesis requirements, uncertainty in clinical outcomes, and the importance of cross-functional planning. These themes form the basis of the key organizational and methodological challenges discussed below.

3. Key Organizational and Methodological Challenges in Oncology JCA Submissions

Drawing from published EU HTA methodological guidance,[3,4,7,8] observations from the first published oncology JCAs,[5,6] and recurring themes identified across these assessments, several organizational and methodological challenges are beginning to emerge. While not intended to be exhaustive, the challenges discussed below represent priority areas for oncology sponsors preparing JCA submissions (**Table 2**).

Table 2. Key Challenges, Implications, and High-Level Best Practices for Oncology JCA Readiness

Challenge	Implication for JCA	High-Level Best Practice
Cross-functional coordination and JCA readiness	Evidence gaps may be identified too late to address effectively	Establish early JCA governance and planning
Broad PICO requirements and comparator complexity	Evidence packages may not address all Member State expectations	Conduct early PICO and comparator mapping
Immature survival evidence and outcome uncertainty	Long-term benefit may be difficult to assess at the time of review	Plan early for OS, HRQoL, and long-term evidence generation
Precision oncology and small patient populations	Limited sample sizes may increase uncertainty	Develop strategies to manage uncertainty and support interpretation

HRQoL: Health-Related Quality of Life; JCA: Joint Clinical Assessment; OS: Overall Survival; PICO: Population, Intervention, Comparator, Outcome.

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Challenge 1: Cross-functional Coordination and JCA Readiness

Beyond methodological issues, successful JCA preparation requires strong operational readiness. Clinical development, health economics and outcomes research (HEOR), regulatory affairs, market access, epidemiology, biostatistics, and medical affairs teams must work together to ensure alignment on evidence-generation strategies and submission requirements. Compressed timelines further increase the importance of cross-functional coordination and early planning.

Challenge 2: Broad PICO Requirements and Comparator Complexity

A key challenge anticipated for oncology JCAs is addressing multiple PICOs that may arise from differences in clinical practice and treatment pathways across Member States. A comparator considered appropriate in one country may not represent the relevant standard of care in another. Consequently, sponsors may need to generate evidence addressing multiple comparators and treatment pathways within a single assessment.[9,10]

Challenge 3: Immature Survival Evidence and Outcome Uncertainty

Many oncology products enter regulatory review before OS data are fully mature. As JCA timelines are closely aligned with marketing authorization, assessors may need to evaluate relative clinical benefit based on intermediate or surrogate endpoints such as PFS, event-free survival (EFS), pathological complete response (pCR), measurable residual disease (MRD), or objective response rate (ORR).[7] Uncertainty regarding the durability and clinical relevance of treatment effects, the impact of crossovers, and limited availability of mature HRQoL and PRO data can make interpretation challenging.[7,8] Sponsors therefore need clear strategies to contextualize surrogate outcomes, characterize uncertainty, and communicate the strengths and limitations of available evidence.

Challenge 4: Precision Oncology and Small Patient Populations

Precision oncology has transformed cancer treatment by enabling therapies targeted toward specific genomic alterations and biomarker-defined populations. However, these populations are often relatively small, creating challenges for statistical power, subgroup analyses, and generalizability of findings.[11] Demonstrating robust and clinically meaningful treatment effects in small populations remains a frequent challenge in oncology assessments.

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4. Practical Considerations and Best Practices for Oncology JCA Readiness

Although experience with oncology JCAs remains limited, several important considerations are becoming increasingly relevant for sponsors preparing evidence packages under the EU HTA framework. While evidence requirements will vary across products and indications, early planning, anticipation of multiple PICOs, robust comparator justification, and transparent management of uncertainty are likely to support JCA preparedness. Based on existing evidence, best practices for oncology JCA readiness are summarized in **Table 3**.

Table 3. Best Practices for Oncology JCA Readiness

Best Practice	Key Actions	Rationale
1. Plan for JCA During Phase II/III Development	Incorporate HTA requirements early; align clinical and market access evidence strategies. [9]	Reduces the risk of evidence gaps and supports alignment between regulatory and HTA requirements.
2. Engage in Early JSC	Seek advice on study design, comparators, endpoints, and evidence plans. [12]	Early consultation helps reduce uncertainty and improve evidence planning.
3. Anticipate Multiple EU PICOs	Conduct early PICO mapping across major EU markets. [9, 10]	Enables preparation of evidence packages that address diverse Member State perspectives.
4. Develop a Robust Comparator Strategy	Map standards of care across Member States and justify comparator choices. [9, 10]	Comparator selection strongly influences assessment of relative clinical benefit.

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Best Practice	Key Actions	Rationale
5. Plan Early for Clinically Meaningful Endpoint Assessment and Reporting	Clearly communicate endpoint maturity, surrogate outcomes, HRQoL/PRO evidence, and long-term follow-up plans.[7]	Supports transparent interpretation of clinical benefit when mature OS data are not yet available.
6. Build an Integrated Evidence Package	Combine RCTs, ITCs, subgroup analyses, and PRO studies where appropriate.[9, 10]	Supports assessment across multiple PICOs and helps address uncertainty.

EU: European Union; HRQoL: Health-Related Quality of Life; HTA: Health Technology Assessment; ITC: Indirect Treatment Comparison; JCA: Joint Clinical Assessment; JSC: Joint Scientific Consultation; OS: overall survival; PICO: Population, Intervention, Comparator, Outcome; PRO: Patient-Reported Outcome; RCT: Randomized Controlled Trial.

5. Strategic implications and Conclusion

The introduction of mandatory JCA represents one of the most significant changes to the European HTA landscape in recent years. As the first major therapeutic area operating under the framework, oncology is providing important insights into how evidence is likely to be assessed under the new EU HTA Regulation.

The first oncology JCAs highlight the importance of early evidence planning, proactive management of PICO and comparator requirements, transparent handling of uncertainty, and strong cross-functional collaboration. Sponsors that integrate these considerations early in development may be better positioned to meet both regulatory and HTA evidence needs.

As additional JCA reports become available, continued learning from published assessments will help refine evidence-generation and submission strategies under the evolving EU HTA framework.

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