CRA Charles River Associates

# Navigating JCA for Orphan Medicinal Products: From scope simulation to pragmatic evidence generation for optimal patient access

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# Table of contents

# Executive summary

The European Union's (EU) Health Technology Assessment (HTA) Regulation has introduced a harmonised approach to evaluating health technologies across Member States. At its core is the Joint Clinical Assessment (JCA), designed to streamline clinical evaluations and improve consistency across national HTA bodies. Central JCA reports are expected to form the future basis for EU Member State national assessments and reimbursement decisions. For Orphan Medicinal Products (OMPs), the JCA will apply from 13th January 2028.

OMPs face unique evidence challenges as care pathways in rare diseases are heterogeneous; comparators may be off-label, absent, or vary by country. Under the JCA, these challenges could be amplified by the complexity of EU population, intervention, comparator, and outcomes (PICO) scoping. For OMPs, PICO heterogeneity and complexity may lead to cumbersome evidence requirements, straining resources and risking partial or irrelevant assessment. Variability in national guidelines and the lack of a standard of care in rare diseases further increase this risk, potentially overwhelming JCA and national HTA processes and delaying patient access.

We suggest a more pragmatic approach to PICO consolidation, including clear communication and simplification to clarify the process for technology developers, facilitating evidence planning and ultimately enhancing JCA report usability.

There is a need for clear, consistent criteria to guide PICO consolidation across different JCAs and assessors/co-assessors as excessive PICOs could introduce unmanageable complexity. The current PICO exercises published by the HTA Secretariat do not provide that clarity. Inclusion of industry health technology developer (HTD) expertise and consideration of real-world complexities also appear to be insufficient currently. HTDs' input is largely limited to written submissions, limiting opportunities for relevant dialogue on evidence challenges, comparator relevance, and methodological exchanges. For rare diseases which are characterised by heterogeneous patient populations, limited natural history data, and often no established standard of care, a formal, flexible established dialogue mechanism with HTDs can help to provide important contextual expertise to help assessors understand disease pathways, treatment goals, and the practical constraints of evidence generation.

For rare diseases, grounding PICO scoping to a limited and manageable number of PICOs will be critical to ensure outputs remain practical, yet meaningful while avoiding an unrealistic burden on limited datasets that adds complexity without improving decisions.

While the JCA is not intended to make value judgements, it should retain flexibility to acknowledge the evidence limitations inherent to OMPs, drawing on principles already embedded in national assessment frameworks that account for uncertainty linked to disease rarity. This would support more contextually relevant evidence interpretation at the national level. Overall, balancing inclusivity with feasibility will be essential to ensure JCA outputs support national HTAs for better and timely patient access.

# Background and objective

The European Union's (EU) Health Technology Assessment (HTA) Regulation, effective from 12th January 2025, introduced a harmonised approach to evaluating health technologies across Member States. A key component of this regulation is the Joint Clinical Assessment (JCA), a process designed to streamline clinical evaluations of new health technologies and improve consistency across national HTA bodies.[1]

The JCA focuses exclusively on clinical effectiveness and safety, producing a single EU-level report that will be available to all Member States. Importantly, national HTA bodies will continue to assess economic, ethical, and societal aspects and make independent decisions on pricing and reimbursement. This dual-level approach aims to reduce duplication while respecting National value judgment criteria and decision-making sovereignty in relation to resource allocation.

For Orphan Medicinal Products (OMPs), the JCA will start to apply in January 2028, following its initial application to oncology medicines and Advanced Therapy Medicinal Products (ATMPs) in 2025.[1]

As the EU HTA framework will apply to OMPs from 2028, this timeline underscores the need to initiate early dialogue now to anticipate and address the unique evidence challenges these products may encounter under future JCAs.

## *The role of PICOs in the JCA process*

A critical element of the JCA is the development of EU **PICOs**, which define the scope and structure of the clinical assessment.[2]

PICOs represent:

- **Population**: The patient group targeted by the health technology
- **Intervention**: The treatment or technology being assessed
- **Comparator(s)**: Alternative treatments, standard of care (SoC), or best supportive care (BSC)
- **Outcomes**: Endpoints used to measure efficacy and safety

PICOs are essential because they set the framework for evidence generation and interpretation. Under the JCA process, the assessor and co-assessor initiate PICO development by sending a structured scoping survey to the HTA bodies of participating Member States. Each HTA body then gathers national input drawing on clinical guidelines, insights from key opinion leaders (KOLs), and internal HTA expertise informed by previous assessments and national decision-making frameworks and submit their responses centrally. In addition, national-level horizon scanning conducted ahead of marketing authorisation may generate research on emerging technologies, which can subsequently inform and feed into HTA body responses to the scoping survey. The assessor and co-assessor consolidate this collective input into a harmonised set of EU PICOs, which forms the basis for the JCA report.[1,2]

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1 European Commission, *Procedural Guidance on Joint Clinical Assessment for Medicinal Products*, accessed January 12, 2026, https://health.ec.europa.eu/publications/procedural-guidance-jca-medicinal-products_en

2 European Commission, *Guidance on the Scoping Process*, accessed January 12, 2026, https://health.ec.europa.eu/publications/guidance-scoping-process_en

However, for OMPs, due to the complexities and challenges of rare disease, even after harmonisation, the consolidated PICOs may still reflect broad variability between Member States. This multiplicity increases the burden on the JCA assessors and health technology developers (HTDs) to address varied evidence requirements and may result in fragmented assessments. If not managed carefully and pragmatically, this could lead to additional analyses being requested at the national level to address unmet evidence needs not resolved during the JCA, causing further delays to patient access and creating greater uncertainty for HTA bodies and payers.

## *Typical evidence challenges for OMPs*

OMPs face distinctive hurdles in generating evidence that meets HTA requirements. These challenges include:

- **Small and heterogeneous patient populations:** Rare diseases individually affect very few patients, making it difficult to recruit large sample sizes for randomised controlled trials (RCTs). Additionally, limited characterisation of the disease and high patient heterogeneity (differences in disease severity, progression, and comorbidities) complicate trial design and interpretation.
- **Endpoints may only partially capture treatment benefit:** In rare diseases, endpoints are often adapted from those used in more common conditions and may not fully reflect the patient experience. As a result, even when therapies deliver meaningful benefit, the available endpoints may only partially capture this impact, making comparative analyses or PICO-based subgroup evaluations challenging and sometimes inconclusive.
- **Reliance on real-world evidence (RWE) and external controls:** Due to ethical and feasibility constraints, rare disease trials frequently use single-arm designs, which may require external controls developed from RWE and retrospective natural history studies, or indirect treatment comparisons (ITCs). RWE is also used to extrapolate clinical trial data beyond the duration of the trial to estimate long-term/sustained benefit.
- **Limited or lack of standardised comparators:** Care pathways in rare diseases are heterogeneous. For many rare diseases, there is no established SoC, only BSC, or treatment approach varies by country due varying availability of treatment options. This challenge is compounded by the variability or complete absence of national clinical guidelines, making it difficult to define appropriate comparators and leading to differences in comparator selection across Member States.

These constraints mean that evidence packages for OMPs often differ significantly from those for more common conditions. Under the JCA framework, these differences could become more pronounced because standard assessment methodologies typically assume, larger patient populations and established clinical pathways, with corresponding expectations for robust comparative evidence. Without adaptation for the rare disease context, JCAs may aggravate, and potentially penalise, features that are inherent to OMP development. As a result, the gap between the evidence generated for OMPs and the expectations embedded in JCA methods may become more visible and challenging to reconcile. For OMPs, PICO heterogeneity and complexity may lead to cumbersome evidence requirements, which strain resources and risk partial or irrelevant assessments.

This work, aims to understand the PICO scoping approach for OMPs, identify associated challenges, and provide insights to support stakeholder preparedness. In doing so, it seeks to generate recommendations that help realise the full potential of the JCA process and inform future updates across relevant EU HTA regulations and guidance.

# Methodology

To explore the implications of the JCA for OMPs, we developed a structured simulation framework to model potential outcomes under the new EU HTA Regulation, based on clinical practice variations and evidence requirements across Germany, France, Italy, Spain, and Sweden. The methodology comprised the following steps:

1. **Design of JCA simulation framework**

   A simulation model was developed to reflect key variables and decision drivers across national HTA processes. This included factors such as national and EU PICO definitions, evidence requirements, and assessment timelines.

2. **Simulation on selected assets and development of national and EU PICOs**

   The JCA PICO scoping process was simulated for two pipeline OMPs:

   - ***OMP 1:*** An asset for an indication with multiple treatment options, including established treatments forming the SoC
     - ***Scenarios:*** Scenario A reflects the broadest feasible label for the new intervention, with Scenarios B and C introducing progressively narrower label restrictions
   - **OMP 2:** An asset for an indication lacking a clear SoC, managed with a variety of treatment options, including off-label therapies but anticipating new entrants
     - **Scenarios:** Scenario A represents accelerated approval‡, while Scenario B reflects standard full approval§

For each asset, a comprehensive process was followed to generate and consolidate PICOs in line with EU HTA guidance:

a. **Initial EU Member State-level PICO generation**
   - Relevant population-intervention-comparator combinations were manually extracted from available HTA and EMA reports for previously approved therapies
   - Where no approved therapies existed in the same indication, local clinical guidelines and evidence from analogous therapies were reviewed to ensure comprehensive coverage of plausible PICO scenarios
   - A broad set of Member State-level PICOs was created to reflect clinical practice variations across Germany, France, Italy, Spain, and Sweden

b. **Application of EU HTA methodological guidance[3]**
   - Standard therapies were grouped to reflect routine SoC use across markets and reduce PICO fragmentation
   - Subpopulations were consolidated based on shared clinical characteristics

[3] European Commission, *Guidance on the Scoping Process*, accessed January 12, 2026, https://health.ec.europa.eu/publications/guidance-scoping-process_en

‡ A pathway allowing earlier authorisation for medicines addressing serious conditions, based on surrogate or intermediate endpoints, with confirmatory evidence required post-approval

§ The conventional pathway where authorisation is granted only after full evidence of safety and efficacy is demonstrated through completed clinical trials

**c. Cross-market harmonisation for development of EU-level PICOs**

- PICOs were first reviewed to align terminology and framing across markets, ensuring consistent definitions of the population, clinical context, intervention, and comparators. This harmonisation step addressed differences in wording, scope, and implicit assumptions to make PICOs directly comparable across countries. Once harmonised, overlapping or duplicative PICOs were consolidated, resulting in a single, coherent set of EU-level PICOs for simulation under the JCA framework

### 3. Expert validation

Finally, CRA conducted double-blinded primary market research interviews with JCA experts and former payers from the national HTA bodies of each country; these discussions validated the simulation assumptions and tested the potential impact of JCA outputs on OMP reimbursement decisions at the national level.

## Results of JCA Simulations for OMPs

Simulations projected between 90 and 234 EU PICOs across modelled scenarios, based on analyses of the five MSs (Germany, France, Spain, Italy, and Sweden), translating into up to ~4,700 analyses per OMP (**Table 1**). While a high degree of overlap in PICO elements was observed across these markets, variation across the wider EU could result in additional PICOs and analyses.

Across the simulations, the scenarios had clear implications for the scale of analyses required. In Simulation 1, where Scenario A reflected the broadest possible label and Scenarios B and C introduced progressively narrower label restrictions, changes to the indicated population directly altered the number of relevant populations. This resulted in substantial variation in the total number of EU PICOs and the associated analytical burden. In Simulation 2, by contrast, modelling accelerated versus full approval did not change the anticipated PICOs in our example; however, differences in approval pathway would impact the availability and maturity of evidence for the analyses. Moreover, while EU PICOs for this simulation remained stable, accelerated versus full approval could affect EU PICOs for other medicines, particularly if approval timing impacts the number of comparators that are applicable (e.g., new comparators enter the market in the case of full approval timelines).

**Table 1: Results from PICO simulations of two OMPs. For OMP 1, Scenario A reflects the broadest feasible label for the intervention, with Scenarios B and C introducing progressively narrower label restrictions. For OMP 2, Scenario A represents accelerated approval, while Scenario B reflects standard full approval.**

| | OMP 1‡ | | | OMP 2‡ |
|---|---|---|---|---|
| **Scenario** | **A** (Broadest label) | **B** (Narrower label) | **C** (Narrowest label) | **A & B** (A = accelerated approval; B = standard approval) |
| **Populations** | 13 | 8 | 5 | 5 |
| **Interventions*** | 2 | 2 | 2 | 1 |
| **Comparators** | 9 | 9 | 9 | 24 |
| **Outcomes** | 20 | 20 | 20 | 22 |
| **Min. # PICOs** | 234 | 144 | 90 | 120 |
| **Min. # of analyses** | **4,680** | **2,880** | **1,800** | **2,640** |

This scale of complexity stems from several factors:

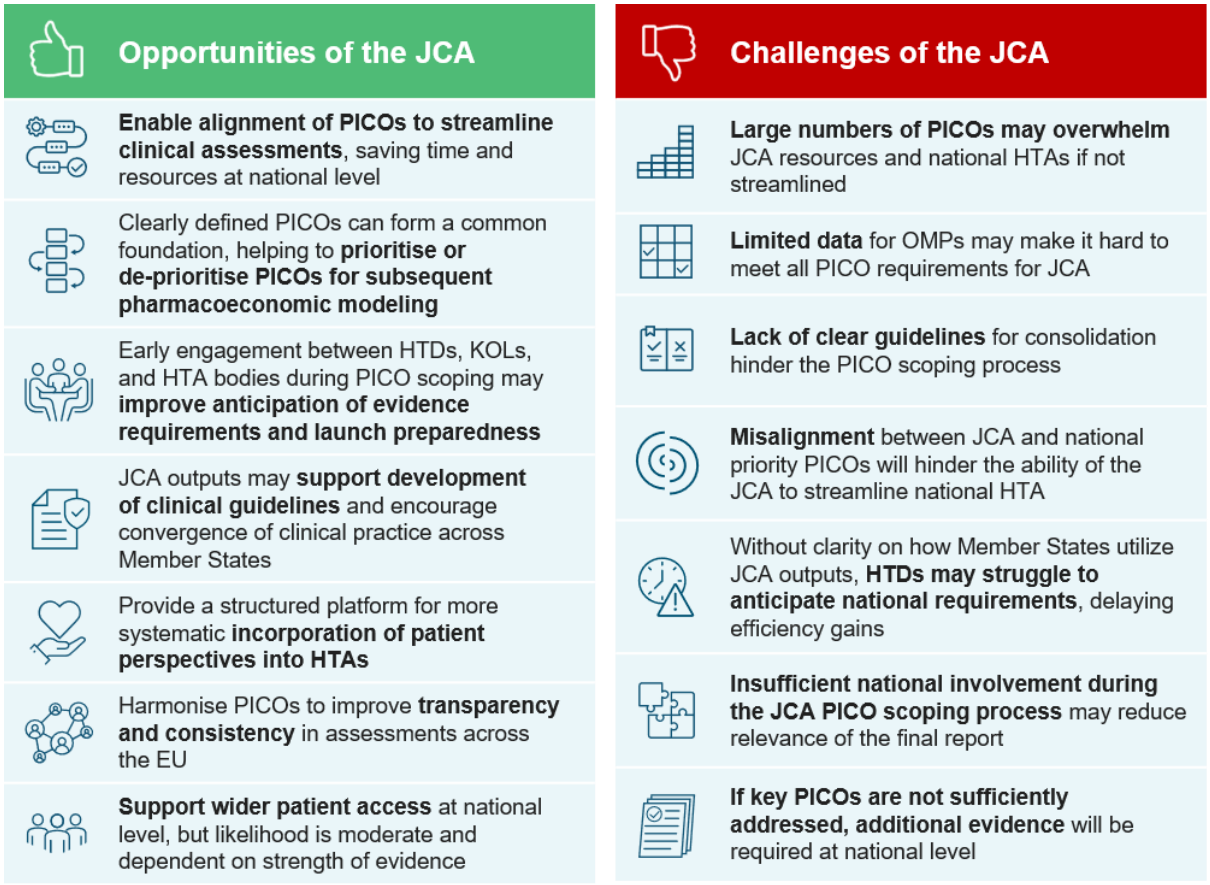
- **P Multiplicity:** Rare diseases often involve multiple clinically distinct populations, each requiring separate consideration
- **C Multiplicity:** In many rare disease contexts, treatment practices vary widely across Member States, leading to multiple comparator options
- **O Multiplicity:** As rare diseases are often less well-characterised and lack clear, established guidelines or precedents from prior market authorisation / HTA processes, Member States frequently request different clinical outcomes and analytical approaches, further increasing variability and multiplying the evidence requirements

Expert validation confirmed that while addressing this scope is theoretically possible, it is practically infeasible beyond ~10 PICOs as evidence availability would limit meaningful interpretation. It remains unclear how assessors and co-assessors would prioritise or narrow down PICOs if the scoping survey were to yield more than this number of clinically important PICOs, including which criteria would be applied and how consistency across markets would be ensured. In practice, assessors are likely to prioritise PICOs based on the availability and robustness of evidence, focusing on comparators within the same class or with similar efficacy and safety profiles, and on populations aligned with the approved label or studied in clinical trials. However, these decision criteria are not explicitly articulated in the EUHTA regulations or guidance documentation, and remain difficult for HTDs to anticipate, particularly given the limited opportunity for manufacturer input during the scoping phase. This uncertainty raises questions around potential trade-offs between feasibility and the utility of the JCA report. Therefore, targeted consolidation is essential for a high-quality JCA, and prioritisation should focus on clinically relevant comparisons, leveraging head-to-head or anchored indirect evidence in distinct populations against a clearly defined SoC.

## Opportunities and challenges of the JCA for OMPs

The simulations highlighted several clear opportunities for the JCA to streamline clinical assessments across the EU, support more efficient decision-making and, ultimately, better patient access. However, the simulations identified some critical challenges that could undermine these benefits if not addressed. **Figure 1** below provides a summary of the key opportunities and challenges.

**Figure 1: Overview of the opportunities and challenges of the JCA identified during the simulations**




### *Key opportunities of the JCA*

The JCA initiative represents a potential major step forward in harmonizing clinical assessments across the EU. Its anticipated benefits include reducing duplication of effort, improving consistency and transparency, and accelerating patient access to innovative therapies. These opportunities are particularly significant:

- Alignment and harmonisation of PICOs across Member States can help streamline clinical assessments, reduce variability in scope and assumptions, and ensure a more coherent basis for decision-making at both EU and national levels
- A single EU-level clinical assessment report improves efficiency for national HTA processes and supports equitable access, which is particularly important in rare diseases, where time to reimbursement is typically longer across many EU countries
- Early national engagement with HTA bodies and KOLs enables better alignment on PICO scoping and evidence planning, fostering predictability, collaboration, and launch preparedness for HTDs

- Transparency and consistency across clinical assessments can strengthen trust in HTA processes and provide a clearer foundation for downstream national assessments, including prioritisation or de-prioritisation of populations, comparators, and outcomes in subsequent pharmacoeconomic modelling and reimbursement decisions
- By consolidating evidence requirements, the JCA can help create a coherent framework for decision-making and, ultimately, support improved patient access; however, this depends on effective implementation both at the EU level, ensuring the JCA process functions as intended, and across Member States
- The structured JCA process also offers an opportunity for more systematic incorporation of patient perspectives into clinical technology assessments
- Ultimately, improving alignment and efficiency, the JCA may support wider patient access at national level; however, the extent of this benefit is likely to be moderate and dependent on evidence strength, as well as effective implementation at both the EU and Member State levels

These goals reflect the positive intent behind the JCA: to speed up access to innovative medicines. However, when it comes into force for OMPs in 2028, it will also be important to ensure the JCA framework is fit for purpose in rare diseases, given the associated evidence generation challenges. Achieving these benefits requires careful implementation and consideration of several key challenges, particularly for OMPs.

## *Key challenges for OMPs with the JCA*

**One of the most significant challenges revealed by the simulations is the potential for complex PICO scoping.** For OMPs, adding just one new comparator or introducing an additional subpopulation does not simply add one more PICO, it can multiply the number of PICOs several-fold. For example, in Simulation 1, Scenario A, expert validation added one additional population and two additional comparators, increasing the total number of PICOs from 168 to 234 and, in turn, raising the number of required analyses from 3,360 to nearly 4,700. Each additional PICO requires separate evidence, analyses, and justification, creating a cascading effect that significantly expands the evidence and analysis burden. This is particularly problematic for OMPs, where data are already limited and difficult to generate. Expert validation confirmed that while large numbers of PICOs are theoretically possible, practical feasibility is constrained by evidence availability, limiting meaningful interpretation. Based on the simulations, even ~10 P-I-C combinations would result in hundreds of analyses (i.e., by requiring an analysis for every outcome per P-I-C, multiplying the P-I-C combinations by the full set of outcomes listed). Therefore, targeted consolidation is essential for a high-quality and usable JCA. Notably, while these simulations were conducted before publication of the first JCA report, the inaugural assessment appears to support the broader concern around PICO breadth and evidentiary feasibility: the JCA for tovorafenib (Ojemda), was structured around 8 PICOs, yet only one PICO was ultimately assessed, reflecting the difficulty of addressing all scoped comparisons in practice.

**The risk of PICO proliferation is further amplified by variability in national guidelines and SoC**. In rare diseases, often there is not a universally accepted SoC, and treatment practices can differ widely across Member States. This variability influences which comparators, populations, and outcomes are considered relevant, leading to a broader and more fragmented set of PICOs during scoping. As a result, the number of PICOs can escalate dramatically, creating an overwhelming evidence requirement that is infeasible to meet for OMPs.

This proliferation of PICOs can overwhelm HTDs, the JCA process and national HTA bodies. In particular, requiring companies to prepare extensive analyses and evidence for multiple potential scenarios upfront, often without clarity on which PICOs will ultimately be retained or deemed relevant, can be burdensome, straining resources and increasing the risk of partial or misaligned assessments.

Consolidating numerous PICOs into a harmonised framework is resource-intensive and time-consuming. If this process is not streamlined effectively, Member States may want to conduct additional assessments at the national level, undermining the goal of harmonisation and delaying patient access.

Beyond PICO complexity, other challenges persist:

- Limited data availability for OMPs, due to small patient populations and reliance on surrogate endpoints, often leaves gaps that cannot meet all PICO requirements
- Misalignment with national priorities, as differences in comparator selection and clinical practice across Member States reduce the relevance of JCA outputs for local decision-making
- Uncertainty around downstream national use of JCA outputs remains a key challenge; without clarity on how Member States will operationalise and give due consideration to JCA reports, health technology developers (HTDs) may struggle to anticipate national requirements, delaying potential efficiency gains

  Insufficient or uneven stakeholder involvement during JCAs may limit local applicability of assessments. While recent efforts have expanded engagement, with the 2025 Annual Report indicating that one patient (or carer) and one clinical expert were involved in each JCA and Joint Scientific Consultations (JSCs)[5], ensuring consistent, meaningful input across stakeholders, including HTA bodies, PAGs, and KOLs, remain critical
- Potential for inconsistent assessments, where unresolved PICOs or unmet evidence requirements lead to duplication of work and further delays at the national level
- Misalignment between initial HTD-proposed indications and final EMA-approved label, as regulatory discussions and negotiations may lead to changes in the target population, comparators, or positioning. This may reduce the relevance of early PICO scoping and evidence plans, requiring later adjustments, creating additional uncertainty for JCAs and downstream national interpretation, and may lead to delays in the final JCA report

Without proactive measures to manage these challenges, the JCA could inadvertently create inefficiencies rather than resolve them, delaying access for patients and discouraging innovation.

5 European Commission, HTACG Annual Report 2025, accessed April 2, 2026, https://health.ec.europa.eu/document/download/45e9328b-f9f4-4d5b-9f5c-385671560785_en?filename=hta_htacg_annual_report_2025.pdf

## Key Recommendations based on simulation results

The JCA is a potential major step toward harmonising HTAs across the EU. For OMPs, however, success will depend on flexibility, both in how EU HTA methodologies are applied, and the interpretation of evidence requirements to account for small patient populations, heterogeneous data, and evolving clinical understanding. Close collaboration among regulators, HTA bodies, industry, HTDs, clinicians, and patient groups is essential to ensure that rare disease-specific challenges are appropriately addressed within the JCA framework. We suggest a more pragmatic approach with the following recommendations outlining suggested priority actions for stakeholders to optimise the JCA process for rare diseases, based on simulation insights and expert interviews. These recommendations will help to ensure that the JCA becomes a catalyst for harmonisation rather than a barrier to access. By fostering collaboration, flexibility, and patient-centred approaches, stakeholders can deliver timely access to innovative therapies and sustain progress in rare disease treatment.

| 1 | **Balance methodological rigor with feasibility in PICO scoping and consolidation to account for rare disease contexts** |
|---|---|

*More streamlined and proportionate PICO scoping can help avoid exponential growth in PICOs, reduce unnecessary evidence demands, and accelerate assessments, while still maintaining assessment quality. In rare diseases, it is particularly important to recognise that evidence generation becomes practically infeasible beyond a limited number of PICO elements, even with ambitious data strategies. Beyond this threshold, evidence becomes too sparse to support meaningful interpretation, limiting the usefulness of assessment outcomes for both EU-level and national decision-making. To better prepare, anticipate, and align with assessor expectations, and ultimately support a robust clinical assessment, health technology developers would benefit from greater clarity on the PICO scoping and consolidation process.*

***Key recommendations:***

- *Clarifying governance and implementation procedures for PICO scoping and consolidation, such as decision-making roles, approaches for resolving assessor divergences, and structured processes for integrating stakeholder contributions, could support early planning and alignment, streamline the scoping process, and reduce the risk of downstream inefficiencies or delays in assessment timelines, product launch, and market access.*
- *Providing greater transparency into how Member States will be surveyed for PICO inputs would be particularly valuable. At present, there is no standardised template for the PICO scoping survey, and it remains unclear whether Member States will be asked a single open-ended question or guided through a more structured set of prompts to support PICO prioritisation.*
- *Given the limited timelines for Member States to respond to PICO scoping requests, a more structured survey approach could help focus inputs, reduce unnecessary proliferation, and facilitate more efficient consolidation by assessors and co-assessors.*
- *Providing clearer guidance during PICO scoping to prioritise approved or well-established comparators could further streamline scoping outputs, ensure clinical relevance, and reduce variation driven by theoretical or low-usage alternatives across Member States.*
- *Greater transparency in PICO consolidation discussions, including clear explanations of how PICOs are derived and why specific comparators are deemed relevant, could help HTDs and other stakeholders understand scoping decisions and improve alignment on evidence expectations.*
- *Providing clearer principles and practical examples for PICO consolidation, informed by experience from early ATMP JCAs, would help prevent unmanageable proliferation of PICOs. These early cases have shown that only a limited number of PICOs can be feasibly supported. Reflecting this reality, particularly in rare diseases, where evidence cannot robustly support excessive PICO numbers, would minimise burden on all parties and enhance the interpretability and value of JCA outputs.*

## 2 Ensure consistency in the application of existing EU HTA methodologies to enhance the relevance of JCA outputs for national HTA and payer decisions

*While EU HTAR provides methodological guidance, differences in how guidance is interpreted, applied, and reviewed by assessors, co-assessors, and Member States involved in drafting and reviewing JCA reports can create variability across JCAs. Strengthening consistency in the interpretation and operationalisation of existing guidance can help minimise duplication, improve predictability, and support national decision-making, ensuring JCA adds value rather than complexity.*

*Greater consistency and clearer criteria to guide PICO consolidation across different JCAs and assessors/co-assessors would help limit excessive PICOs and reduce unmanageable complexity. Unfortunately, the current PICO exercises published by the HTA Secretariat do not provide that clarity.*

***Key recommendations:***

- *The Member State Coordination Group on HTA (HTACG) could consider providing additional guidance to all stakeholders involved in the JCA process to support more consistent interpretation of existing guidance among assessors and co-assessors, as well as across Member States reviewing and commenting on JCA drafts.*
- *It may be helpful to acknowledge that RCTs are not always feasible in rare disease contexts. Guidance could emphasise consideration of ethical, clinical, and practical factors when RCT evidence is not possible, recognise the relevance of alternative evidence sources (e.g., real-world evidence, external control arms), and clarify that clinical trial designs endorsed and/or accepted by the EMA should be regarded as relevant evidence for the purposes of JCA and subsequent national decision-making, drawing on applicable experience across Member States.*
- *Current JCA methodologies could further highlight how to account for contextual factors such as unmet need, small patient populations, and limited evidence availability to support more consistent JCAs.*
- *While the JCA is not intended to make value judgements, providing clearer guidance on how JCAs can flexibly acknowledge and transparently present evidence limitations inherent to OMPs, drawing on principles already embedded in national assessment frameworks, would support more contextually relevant interpretation of evidence at the national level.*

## 3 Ensure PICOs and JCA reports reflect real-world patient needs and clinical practice

*Greater stakeholder involvement, including KOLs, patients and industry, to improve relevance, credibility, and acceptance of JCA outputs at the national level, while maintaining a manageable and aligned PICO framework across Member States is important in rare diseases where clinical guidelines are often lacking, and evidence generation is challenging. For rare diseases, which are characterised by heterogeneous patient populations, limited natural history data, and often no established standard of care, current JCA frameworks may insufficiently capture real-world clinical complexities. Moreover, opportunities for dialogue within the current JCA process appear suboptimal, often limited to written exchanges rather than meaningful, iterative engagement, restricting the ability of HTDs to contextualise evidence challenges, comparator relevance, and methodological constraints.*

***Key recommendations:***

- *Greater transparency on how stakeholder input (from HTDs, PAGs, KOLs, and scientific societies) informs PICO determination and consolidation and final JCA report could support shared understanding and alignment.*
- *Building on recent progress, the HTACG could endorse and further promote systematic patient and clinician involvement when member states develop their PICOs, ensuring inputs are representative of EU real-world clinical practice, particularly in areas without established clinical guidelines. Increased availability of structured interactions with industry, where appropriate (e.g., JSCs), taking into consideration the evidence challenges faced by OMPs could strengthen the real-world relevance of JCAs. This could include establishing structured, iterative advice meetings with HTDs at key milestones (e.g., pre-PICO scoping, pre-submission, and clarification stages), enabling timely exchange of contextual expertise on disease pathways, treatment goals, and evidence generation constraints.*

- *The HTACG could provide resources, such as plain language summaries, guidance, and training to support meaningful participation from all stakeholders.*
- *While national submissions ultimately determine how patient experience and outcomes are incorporated locally, the HTACG could encourage recognition of rare disease patient experiences and outcomes in guidance documents and assessment templates. In addition, fostering earlier and continuous dialogue, particularly in rare diseases where knowledge gaps are substantial, could reduce uncertainty, focus analyses on outcomes most relevant to Member States, and better align expectations around post-launch evidence generation.*

## 4 Apply learnings from early JCAs and embed continuous feedback mechanisms to optimise JCA processes

*Tailored approaches, supported by continuous feedback and learnings from early JCAs, can help ensure the JCA framework evolves in a way that supports equitable access for rare disease patients. If applied rigidly, a JCA approach focused primarily on long-term durability and randomised controlled evidence could have excluded a substantial proportion of currently authorised OMPs, many of which were approved on the basis of alternative endpoints, non-RCT designs, or limited follow-up at launch.*

*As a general guiding principle, for rare diseases, JCA PICO rules should build on what already works in member states to create a more operational, predictable, and effective framework for expert involvement in OMP assessments. For sustained and improved rare disease access across the EU, it is therefore critical that the JCA explicitly acknowledges and builds on the value-assessment frameworks used in more advanced Member States, which already recognise and integrate disease-rarity-driven evidence uncertainty.*

*Drawing on early experiences (e.g., ATMPs, rare oncology) and creating structured mechanisms for ongoing dialogue can further help to refine methodologies, address evidence constraints, and prevent systemic barriers over time.*

*For the EU ecosystem, clarity on a more pragmatic approach would also send a strong signal that the EU, through the JCA, is progressing towards an innovation-enabling and forward-looking HTA framework, rather than reverting to more restrictive and fragmented approaches.*

***Key recommendations:***

- *Gathering and applying learnings from early JCAs, including ATMPs and rare oncology, may help to inform future updates to guidance, support refinement of assessment practices, and promote greater consistency across assessor-co-assessor teams for upcoming rare disease evaluations.*
- *While external engagement mechanisms (e.g. roundtables and consultations) are already in place, more meaningful and structured involvement could be achieved through expanded availability and use of JSCs, allowing early discussion of evidence challenges, feasibility constraints, and potential completion approaches for OMPs.*
- *Although opportunities exist within the JCA submission process for stakeholder involvement, enhancing the depth and structure of these exchanges would allow rare disease-specific constraints, for example, limited evidence availability or methodological feasibility challenges, to be more meaningfully reflected in HTACG guidance, templates, and assessor briefings, reducing the risk of systemic barriers.*
- *The HTACG could also facilitate best-practice sharing across Member States with dedicated rare-disease or OMP value frameworks, enabling the JCA to leverage existing experience in managing uncertainty, rather than resetting expectations at EU level.*
- *At the national level, the EU Commission could play a stronger enabling role by encouraging Member States to share their national PICOs with HTDs once the JCA scope is finalised, or at the latest at the point of JCA submission. Greater transparency and alignment on national evidence needs would support more timely, relevant, and efficient national assessments following the JCA.*
- *Developing or enhancing mechanisms for regular collaboration and process refinement, by building on early learnings and offering transparency on how feedback is considered, could support more proportionate, predictable, and efficient JCA processes over time and ahead of the planned 2028 review.*

## About Charles River Associates

Charles River Associates is an economic consultancy that specialises in public policy issues in the life sciences industry. CRA has undertaken many assessments of challenges facing particular medicines and the case for policy reform. CRA focuses on delivering high-quality, robust analysis in a compelling fashion that is accessible to the target audience. CRA has worked for the industry (through EFPIA, PhRMA, and IFPMA), national trade associations, and individual companies on a wide range of issues over the last 15 years.

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