Joint Clinical Assessments for Rare Disease Therapies: Lessons from the First EU JCA Experience

What the Tovorafenib Assessment Reveals About Comparator Selection, Evidence Gaps, and Uncertainty Under the EU HTA Regulation

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Introduction

The implementation of the European Union Health Technology Assessment Regulation (HTAR) marks a significant change in how clinical evidence is evaluated across Europe. Through the Joint Clinical Assessment (JCA), selected medicines undergo a single EU-level assessment of their relative clinical effectiveness and safety, creating a common evidence foundation that Member States can use during national health technology assessment (HTA) processes. Although pricing and reimbursement decisions remain national responsibilities, the JCA is intended to reduce duplication and improve consistency in clinical evidence assessment across Europe.[1]

For manufacturers, the JCA introduces both opportunities and challenges. While a single assessment may streamline aspects of evidence review, manufacturers must now generate evidence that is relevant across multiple healthcare systems, clinical practices, and comparator expectations.

These challenges are particularly pronounced in rare diseases, where evidence generation is often constrained by small patient populations, limited comparative data, heterogeneous disease presentations, and practical barriers to conducting randomized controlled trials.[2–4]

The recently published JCA for tovorafenib in pediatric low-grade glioma (LGG) provides the first real-world illustration of how these challenges may be evaluated under the HTAR framework.[5] The assessment offers important insights into comparator selection, indirect evidence requirements, real-world evidence (RWE) limitations, and management of uncertainty that are likely to be relevant across many rare disease submissions.

The Central Challenge: Comparator Selection Across Multiple Member States

The JCA process is built around PICO-based assessment questions that define the populations, interventions, comparators, and outcomes that will be evaluated. These PICO questions ultimately determine the evidence manufacturers are expected to provide.[1]

For many rare diseases, standards of care vary substantially across Europe. As a result, a therapy may face multiple relevant comparators rather than a single universally accepted standard of care.

The tovorafenib JCA provides a clear example of this challenge. For the full indicated population of pediatric LGG patients with BRAF alterations who had received prior systemic therapy, the assessment scope included an individualized treatment comparator comprising multiple treatment options, including:

- Vinblastine
- Carboplatin plus vincristine
- Bevacizumab-containing regimens
- Everolimus
- Dabrafenib plus trametinib
- Other treatment combinations considered relevant across Member States[5]

This broad comparator framework reflects differences in clinical practice across European healthcare systems. However, it also creates a significant evidence-generation challenge because pivotal development programs are rarely designed to address every comparator that may later be considered relevant during HTA assessment.

For manufacturers developing rare disease therapies, the implication is clear: understanding likely comparator expectations early in development is becoming increasingly important. Evidence-generation strategies that focus solely on regulatory requirements may not adequately address future HTA evidence needs.

When Clinical Activity Is Not Enough: The Importance of Comparative Evidence

Demonstrating treatment activity is often feasible in rare diseases through single-arm studies. Demonstrating comparative effectiveness is considerably more difficult.
This distinction emerged clearly in the tovorafenib JCA. The assessors reported that neither randomized controlled trials directly comparing tovorafenib with the relevant comparators nor studies enabling anchored indirect comparisons were identified for any of the assessment PICOs.[5]

Consequently, no comparative effectiveness or safety analyses were available for most of the assessment scope. Specifically, the report concluded that no comparative evidence was available for PICOs 1–4, 6, and 8.[5]

Although the developer submitted single-arm data from the pivotal FIREFLY-1 study, the JCA report explicitly states that these data were not included in the assessment because they did not provide information on the relative effectiveness or safety of tovorafenib compared with the comparators defined in the assessment scope.[5]

This finding highlights an important principle of the JCA process i.e., Strong evidence of clinical activity may not be sufficient if comparative evidence is lacking. For rare disease therapy manufacturers, this reinforces the need to consider comparative evidence requirements early rather than viewing them as a challenge that can be addressed after pivotal trial completion.

The Promise and Limitations of Indirect Comparisons

Because randomized head-to-head trials are often impractical in rare diseases, indirect comparison methods frequently become an important component of evidence-generation strategies.

The tovorafenib assessment demonstrates both the value and limitations of these approaches.

For one subgroup of patients with BRAF V600E-mutated disease, the manufacturer submitted an unanchored matching-adjusted indirect comparison (MAIC) comparing tovorafenib with dabrafenib plus trametinib.[5]

This represented the only comparative evidence ultimately included within the assessment.

While MAICs and related population-adjusted approaches can provide useful comparative insights when direct evidence is unavailable, they rely on strong assumptions regarding population comparability and adjustment for prognostic factors. These assumptions become increasingly difficult to satisfy when sample sizes are small, a common challenge in rare diseases.

The experience from the first JCA therefore suggests that indirect comparisons may play an important role in future submissions, but they are unlikely to eliminate uncertainty entirely.

Manufacturers should anticipate that the robustness of indirect evidence will receive substantial scrutiny and should ensure that assumptions, limitations, and potential biases are transparently described.

RWE Is Important—but Fit-for-Purpose Data Remain Difficult to Obtain

RWE is frequently proposed as a solution to evidence gaps in rare diseases, particularly when randomized comparative studies are infeasible.

The tovorafenib submission provides a useful case study of both the potential and limitations of this approach.

According to the JCA report, the manufacturer explored the creation of external control arms using patient data acquired outside clinical trials. A feasibility assessment was conducted to identify suitable real-world data sources capable of supporting comparative analyses.[5]

However, despite identifying a potentially relevant database, the manufacturer ultimately concluded that available data were insufficient because of limited numbers of appropriately characterized patients and inadequate follow-up within the target population.[5]

As a result, no fit-for-purpose external control source could be established.

This experience illustrates a challenge that many rare disease therapy manufacturers are likely to encounter. While the theoretical value of RWE is widely recognized, the practical availability of sufficiently robust data remains limited in many rare conditions.

Consequently, manufacturers should consider investing in evidence infrastructure well before launch, including:

- Disease registries
- Patient registries
- Natural history studies
- Long-term observational cohorts
- Post-authorization evidence-generation programs

These initiatives may ultimately determine whether meaningful comparative analyses can be conducted during future JCA assessments.

Managing Uncertainty Throughout the Product Lifecycle

A recurring theme throughout rare disease development is uncertainty. Small sample sizes, limited follow-up, evolving standards of care, and challenges in comparator selection often create evidence limitations that cannot be fully resolved before launch. The JCA framework does not eliminate these challenges. Instead, it creates a structured process for evaluating them.

The tovorafenib assessment demonstrates that uncertainty becomes particularly important when comparative evidence is limited. Even where clinical activity is demonstrated, uncertainty regarding relative effectiveness may remain substantial if suitable comparator data are unavailable.[5]

Manufacturers should therefore view uncertainty management as a lifecycle activity rather than a submission-stage exercise. A comprehensive evidence strategy may include:

- Early scientific dialogue
- Anticipatory PICO planning
- Comparative evidence development
- Natural history studies
- Registry-based evidence generation
- Long-term follow-up programs
- Post-launch evidence collection

The objective should not necessarily be to eliminate uncertainty entirely, which may be impossible in many rare diseases, but rather to characterize and reduce uncertainty as effectively as possible over time.

Patient-Centered Evidence Remains Essential

While comparative effectiveness is central to the JCA process, patient-centered outcomes remain critical for understanding the broader impact of treatment. Rare diseases often affect multiple dimensions of patients' lives that may not be fully captured by traditional clinical endpoints. Patient-reported outcomes and other patient-centered measures can provide valuable information regarding:

- Quality of life
- Functional status
- Symptom burden
- Daily activities
- Emotional well-being
- Caregiver burden

Incorporating patient perspectives into evidence-generation programs may help contextualize treatment benefits and support interpretation of clinical findings, particularly when conventional efficacy endpoints provide only a partial picture of disease burden.

Key Lessons from the First JCA Experience

Rare Disease JCAs May Be Constrained by Comparator Evidence Rather Than Clinical Evidence

The first JCA experience with tovorafenib demonstrates that generating comparative evidence may be more challenging than demonstrating clinical activity in rare diseases. Although clinical benefit was observed in the pivotal single-arm FIREFLY-1 study, comparative effectiveness could not be assessed for most PICOs because suitable comparator data were unavailable. This highlights a fundamental challenge for rare disease developers: regulatory evidence may be sufficient to support approval, while comparative evidence required for HTA assessment may remain limited or absent.[5]

The Absence of a Common Standard of Care Amplifies JCA Complexity

Unlike many common diseases, rare diseases frequently lack a universally accepted standard of care. In the tovorafenib JCA, multiple treatment options were included within the comparator framework, reflecting variation in clinical practice across Member States.[5] This illustrates how longstanding uncertainty regarding appropriate comparators in rare diseases may become amplified under the JCA framework, where a single assessment must address evidence needs across multiple healthcare systems.

Rare Disease Evidence Infrastructure Must Be Built Before Submission

The tovorafenib assessment also demonstrated the limitations of attempting to retrospectively generate comparator evidence. Despite efforts to construct external control cohorts, suitable real-world data sources could not be identified because of limited patient numbers and insufficient follow-up.[5] For rare disease therapies, this reinforces the importance of investing early in registries, natural history studies, and long-term observational data collection, as these evidence sources may ultimately determine the feasibility of future comparative effectiveness assessments.

Conclusion

The first Joint Clinical Assessment conducted under the EU HTAR framework offers important insights into the evidence challenges likely to face rare disease therapies.

The experience suggests that the defining challenge of future rare disease JCAs may not be demonstrating clinical activity, but rather generating evidence capable of addressing multiple comparator expectations across Europe when comparative data are inherently limited.

The tovorafenib assessment illustrates how comparator selection, indirect comparisons, RWE availability, and uncertainty management may influence JCA outcomes. As a result, manufacturers should begin integrating HTA evidence requirements much earlier in development than has historically been necessary.

Organizations that proactively align clinical development, comparative effectiveness research, RWE generation, and patient-centered outcomes planning will be better positioned to support robust JCA submissions and facilitate informed decision-making across European healthcare systems.

References

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