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Are Rare Disease Clinical Trials Ready for EU Joint Clinical Assessment (JCA)?

Mojgan Gitimoghaddam[1], Gaurang Nazar[1], Mir-Masoud Pourrahmat[1], Massoud Toussi[2], Mir Sohail Fazeli[1]
[1]Evidinno Outcomes Research Inc., Vancouver, BC, Canada
[2]United BioSource LLC, Paris, France

Background

- Regulation (EU) 2021/2282 established a European Union (EU)-level framework for joint clinical assessment (JCA) of the relative effects of health technologies on health outcomes.[1]
- JCAs commenced on 12 January 2025 for new oncology medicines and advanced therapy medicinal products, with orphan medicinal products entering scope from 13 January 2028.[1]
- A JCA evaluates available clinical evidence against assessment scopes defined by population, intervention, comparator, and outcome (PICO) questions relevant to Member States.[1]
- Member State guidance stresses patient-relevant outcomes, sound measurement properties, appropriate handling of composite outcomes, and explicit uncertainty around surrogate endpoints.[2]
- Rare-disease programs face small, heterogeneous populations, sparse natural-history data, and ethical constraints on randomization.
- These constraints often necessitate single-arm or externally controlled designs and may limit the availability of patient-reported and mature long-term evidence.

Objective

- To assess the alignment of pivotal rare-disease trials with EU JCA evidence expectations for comparative study design, comparator selection, patient-relevant endpoints, patient-reported outcomes and health-related quality of life, and evidence maturity.

Methods

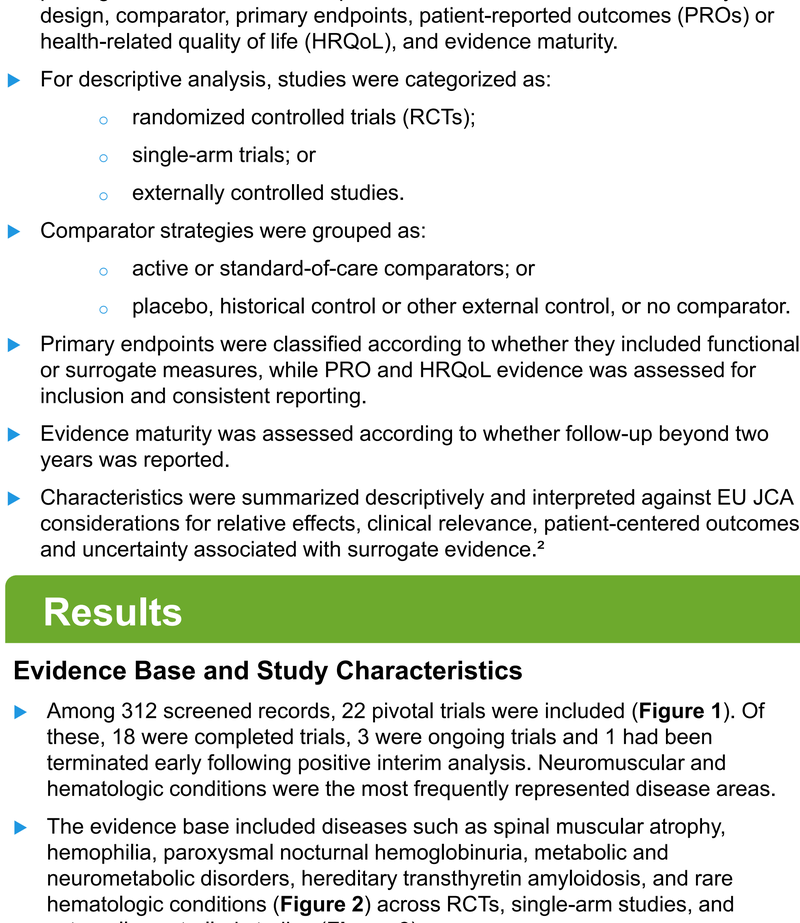
- A targeted literature review (TLR) was conducted for publications from January 2015 through March 2025, using PubMed, ClinicalTrials.gov, and European Medicines Agency (EMA) European Public Assessment Reports (EPARs).
- Search terms and phrases included “rare diseases”, “orphan diseases”, “pivotal trial”, “clinical trial”, “comparative study”, and “patient-reported outcomes”.
- Eligible records reported registration-enabling clinical trials or pivotal evidence packages in rare diseases and provided extractable information on study design, comparator, primary endpoints, patient-reported outcomes (PROs) or health-related quality of life (HRQoL), and evidence maturity.
- For descriptive analysis, studies were categorized as:
  - randomized controlled trials (RCTs);
  - single-arm trials; or
  - externally controlled studies.
- Comparator strategies were grouped as:
  - active or standard-of-care comparators; or
  - placebo, historical control or other external control, or no comparator.
- Primary endpoints were classified according to whether they included functional or surrogate measures, while PRO and HRQoL evidence was assessed for inclusion and consistent reporting.
- Evidence maturity was assessed according to whether follow-up beyond two years was reported.
- Characteristics were summarized descriptively and interpreted against EU JCA considerations for relative effects, clinical relevance, patient-centered outcomes, and uncertainty associated with surrogate evidence.[2]

Results

Evidence Base and Study Characteristics

- Among 312 screened records, 22 pivotal trials were included (**Figure 1**). Of these, 18 were completed trials, 3 were ongoing trials and 1 had been terminated early following positive interim analysis. Neuromuscular and hematologic conditions were the most frequently represented disease areas.
- The evidence base included diseases such as spinal muscular atrophy, hemophilia, paroxysmal nocturnal hemoglobinuria, metabolic and neurometabolic disorders, hereditary transthyretin amyloidosis, and rare hematologic conditions (**Figure 2**) across RCTs, single-arm studies, and externally controlled studies (**Figure 3**).
- Interventions encompassed diverse modalities, including antisense oligonucleotides and gene therapies.[3,4]

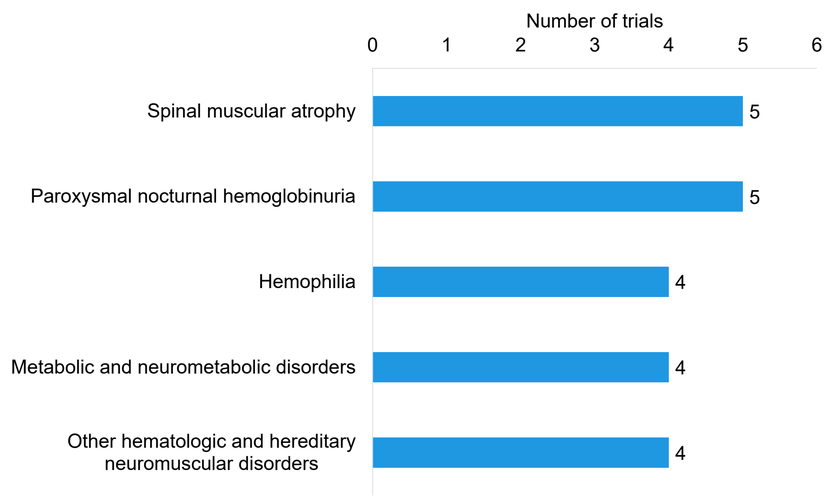
Figure 1. Selection of pivotal rare-disease trials



EMA: European Medicines Agency; EPAR: European Public Assessment Report

Results (continued)

Figure 2. Distribution of included trials by disease area

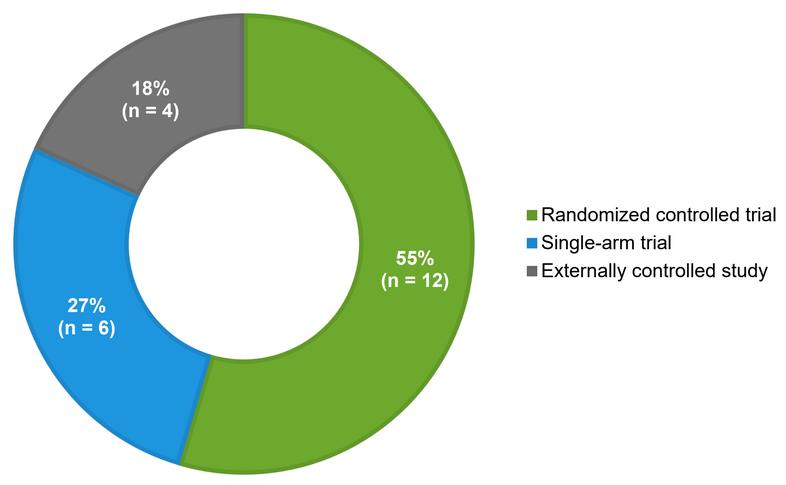


The “other hematologic and hereditary neuromuscular disorders” category includes rare hematologic malignancies, EBV-positive post-transplant lymphoproliferative disease, and hereditary transthyretin amyloidosis with polyneuropathy.

Trial Design Landscape

- Twelve trials (55%) were RCTs (**Figure 3**).
- Ten trials (45%) were non-randomized, comprising six single-arm studies and four externally controlled studies.
- Non-randomized evidence occurred in several gene- and cell-therapy programs and ultra-rare populations.
- Externally controlled approaches included natural-history cohorts, historical placebo groups, and prospective or intra-patient lead-in comparisons.[4-6]

Figure 3. Distribution of trial designs among included studies



Externally controlled studies included trials using nonconcurrent historical or natural-history controls and prespecified comparative lead-in evidence.

Comparator Landscape

- Ten trials (45%) used active or standard-of-care comparators, including direct comparison trials such as COMMODORE 2[7] and COMET.[8]
- Twelve trials (55%) relied on placebo, historical controls or other external controls, or no comparator.
- The absence of a direct comparison with a clinically relevant treatment may limit the ability of a trial to answer all PICO questions specified during an EU JCA.
- Some single-arm programs provided compelling evidence of treatment activity but did not directly estimate relative effects against therapies used in contemporary clinical practice.

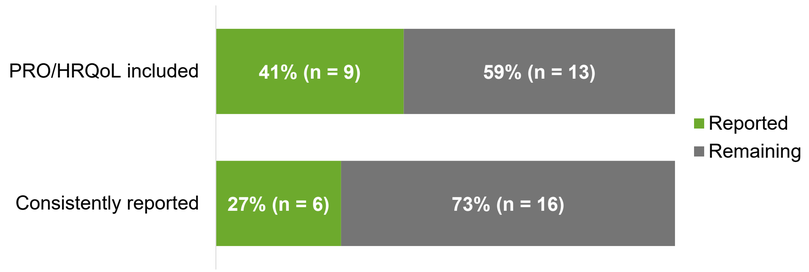
Endpoint Landscape

- Primary endpoint selection varied substantially across disease areas.
- Functional or surrogate endpoints were used in 13 trials (59%), including motor-function, respiratory-function, hematologic, and biochemical outcomes.[8,9]
- Definitive clinical outcomes were less frequent, which may increase uncertainty when the relationship between a measured endpoint and long-term patient benefit is incompletely established.
- The Health Technology Assessment Coordination Group outcomes guidance recommends evaluating the clinical relevance of outcomes and explicitly characterizing the evidence supporting surrogate relationships with patient-centered outcomes.[2]

Patient-Reported Outcomes (PROs) and HRQoL

- PROs or HRQoL were included in 9 trials (41%). These outcomes were consistently reported in only 6 trials (27%) (**Figure 4**).
- Reported instruments assessed domains such as fatigue, physical function, independence, symptoms, treatment burden, and overall quality of life.
- Inconsistent prespecification, incomplete reporting of missing data, and absence of interpretable responder thresholds may limit the contribution of patient-reported evidence to comparative assessment.

Figure 4. Inclusion and reporting of PRO/HRQoL evidence



HRQoL: health-related quality of life; PRO: patient-reported outcome.

Evidence Maturity

- Only 8 trials (36%) reported follow-up beyond two years. Limited follow-up was particularly relevant for one-time gene therapies, cell therapies, and treatments intended to provide durable disease modification.[4,5,10]
- Immature evidence can create uncertainty regarding persistence of treatment effect, late adverse events, durability of response, treatment waning, and the need for subsequent therapy.

Table 1. Evidence characteristics relevant to EU JCA

Domain	Observed evidence	Potential implication for JCA
Design	**55% RCTs, 45% non-randomized**	Relative-effect certainty varies
Comparator	**55% lacked active/SOC comparator**	PICO mismatch risk
Endpoints	**59% functional/surrogate**	Clinical relevance may require justification
PRO/HRQoL	**41% included; 27% consistently reported**	Patient-centered evidence limited
Evidence maturity	**36% >2-year follow-up**	Durability uncertainty
Evidence integration	**Heterogeneous evidence packages**	Additional evidence may be required

HRQoL: health-related quality of life; JCA: joint clinical assessment; PICO: population, intervention, comparator, outcome; PRO: patient-reported outcome; RCT: randomized controlled trial; SOC: standard of care.

Key JCA Evidence Gaps

- **Comparator gap:** More than half of the included trials did not provide a direct comparison with an active or standard-of-care treatment.
- **Outcome gap:** Functional and surrogate outcomes were more frequent than definitive clinical outcomes.
- **Patient-evidence gap:** PRO/HRQoL measures were included in fewer than half of the trials and consistently reported in only 27%.
- **Maturity gap:** Fewer than four in ten trials reported follow-up beyond two years.

Implications for Evidence Generation

1. **Map JCA PICO questions early.** Populations, comparators, and patient outcomes should shape pivotal-trial design before it is fixed.
2. **Prioritize direct comparative evidence.** Use active or standard-of-care comparators where scientifically and ethically feasible.
3. **Justify endpoints.** Demonstrate clinical relevance and surrogate-to-benefit relationships for surrogate and composite outcomes.
4. **Prespecify patient-reported evidence.** Use appropriate instruments and report completion, effect size, uncertainty, and responder thresholds.
5. **Plan for maturity.** Use long-term follow-up, registries, and post-authorization evidence to evaluate durability and late safety.
6. **Align regulatory and HTA planning.** Early coordination may reduce evidence gaps.
7. **Recognize rare-disease constraints.** JCA implementation should balance evidentiary rigor with the practical limitations of rare-disease trial design.

Conclusions

- Rare-disease pivotal trials frequently exhibit characteristics that may increase uncertainty in EU JCA.
- Although 55% of included trials were randomized, only 45% used active or standard-of-care comparators, and functional or surrogate endpoints were used in 59%.
- PRO/HRQoL evidence and follow-up beyond two years were reported inconsistently, potentially limiting assessment of patient-relevant and durable benefit.
- These characteristics reflect genuine constraints in rare-disease evidence generation and may make comparative effectiveness more difficult to establish across the PICO scopes requested by Member States.
- Earlier integration of relevant comparator strategies, patient-centered endpoints, interpretable surrogate evidence, and longer-term follow-up will be important for supporting future EU JCA and national reimbursement decisions.

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Email: mpourrahmat@evidinno.com

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