The importance of rare disease-specific procedures in HTA processes in ensuring equitable access to orphan products as a result of EU JCA

Adelaide Shaw-Maguire, Cameron Huke, Georgia Roberts, James Wantling, Andrew Mumford
Initiate Consultancy, London, UK.

SUMMARY

OBJECTIVES

- The EU Joint Clinical Assessment (JCA) is due to come into effect for oncology products and Advanced Therapy Medicinal Products (ATMPs) in January 2025, and to become a requirement for orphan medicines as of January 2028.[1]
- This targeted review (TR) considers whether these new Health Technology Assessment (HTA) processes will appropriately consider the unique challenges associated with achieving access for orphan products for rare diseases.

METHODS

- A TR was conducted of the published methods guidance for EU JCA to identify the presence (or lack) of rare disease-specific processes and considerations which are included in current national-level HTA-body processes.
- The potential impact of the presence or lack of said processes were assessed in relation to a semi-quantitative analysis of orphan-specific factors affecting HTA and to the likelihood of successful HTA outcomes for orphan products observed across ten key European markets in 2023 and Q1-Q2 2024.

FINDINGS

- In 2023 and Q1-Q2 2024, orphan products had lower reimbursement success rates compared to non-orphan products assessed through standard HTA processes.
- Orphan products assessed through dedicated orphan-specific HTA processes had a greater reimbursement success rate compared to orphan products assessed in standard HTAs.
- A greater extent of consideration of orphan-specific factors in HTA processes was associated with higher reimbursement success rates for orphan products.

BACKGROUND & AIMS

- In January 2022, EU parliament passed a new EU HTA regulation act for an HTA working structure for Europe,[2] which will govern the European cooperation between regulators and HTA bodies, replacing the voluntary JCA system.[3]
- The regulation aims to enhance access to innovative health technologies and strengthen the quality and efficiency of HTA across the Union.[4]
- The HTA regulation applies at the European level for oncology products and ATMPs as early as 12th January 2025. Orphan products will require EU JCA from January 2028, and all other medicines launching in the EU will require EU JCA from January 2030.[1]
- This work aims to compare and contrast the TR of the EU JCA guidelines with analyses of current orphan-specific HTA, to determine if the EU JCA guidelines are appropriate for orphan products in reflecting key considerations in the current orphan HTA processes across European and UK countries.

METHODS

- Six EU JCA HTA guidance documents,[5] were analysed in a TR for orphan-specific criteria or criteria that were probable to affect orphan products in HTAs.
- Key areas identified in the HTA guidance include: certainty of results, observational studies, prospective vs. retrospective analysis, single-arm trials and surrogate outcomes.
- To compare how these EU JCA guidance relate to current practice, a semi-quantitative analysis was performed on ten key HTA markets (Denmark, England, France, Ireland, Italy, Netherlands, Norway, Scotland, Spain, and Sweden), giving modified weights to aspects of HTA that could influence orphan products in HTA reimbursement, with a higher rank equaling greater consideration. An approximate ranking of countries was then generated based on willingness to consider orphan-specific HTA aspects.
- Alongside this, HTA recommendations for orphan products in the same HTA markets in 2023 and Q1-Q2 2024 were reviewed, and data were collated describing the reimbursement success rates in each market*.

RESULTS

EU JCA clinical study guidance (CSG): **"**It is methodologically inappropriate, for example, to take the rareness of a disease or the impossibility of blinding as a justification to ignore the resulting uncertainties in the clinical evidence.[6]**"**

Findings from TR of EU JCA guidance

- *Severity modifiers*: the quote above from the EU JCA CSG,[6] highlights the EU JCA committees' position on showing a lack of willingness to account for the realities and challenges of orphan products in HTA. These realities can be considered most explicitly as severity modifiers but are not discussed at all throughout the six documents.
- *Observational studies (OS):* the EU JCA CSG highlights that OS only allow for the assessment of relative effectiveness of interventions used in current medical practice, i.e. not for new interventions.[6] OS are used widely for orphan products, often there is no/limited standard of care, so interventions being studied are typically new. Therefore, common OS types in their current form are effectively excluded.
- *Retrospective vs. prospective:* a clear preference for prospective analysis was described in terms of suggesting high recall bias from retrospective studies.[6] Issues arise from this for orphan trials as due to rarity the populations may be so small that data acquisition requires very long timelines, and the population may additionally have shorter life expectancies.
- *Single-arm trials:* described as having a lower importance for relative effectiveness assessment in HTA, and therefore not needing any rules.[6] This guidance is in severe conflict with the reality of the frequency of single-arm trial use in orphan disease.
- *Surrogate outcomes:* in the EU JCA there appears to be a willingness to accept surrogate outcomes as long as they are a long-term or final outcome, and the specific EU member state finds it appropriate.[7]

Results from analyses of current European & UK orphan practice

- Reimbursement success rates were compared for products with and without EMA orphan designation assessed through standard HTA processes (i.e., not orphan-specific) in 10 key HTA markets. In 2023 and Q1-Q2 2024, orphan products had a lower likelihood of successful reimbursement compared to non-orphan products when assessed through standard HTA processes (Figure 1).
- Further analysis was conducted to assess the impact of dedicated orphan-specific assessment processes on the likelihood of reimbursement success for orphan products. Orphan products assessed through orphan-specific processes had a higher likelihood of successful reimbursement compared to orphan products assessed through standard HTA processes (Figure 2).

Figure 1: Reimbursement success rates for orphan and non-orphan products assessed through standard HTA processes

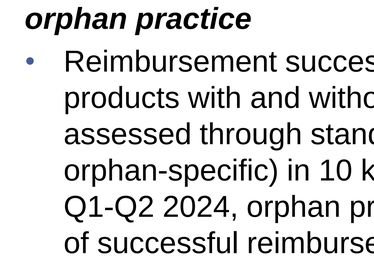
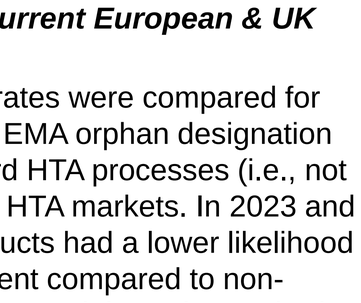


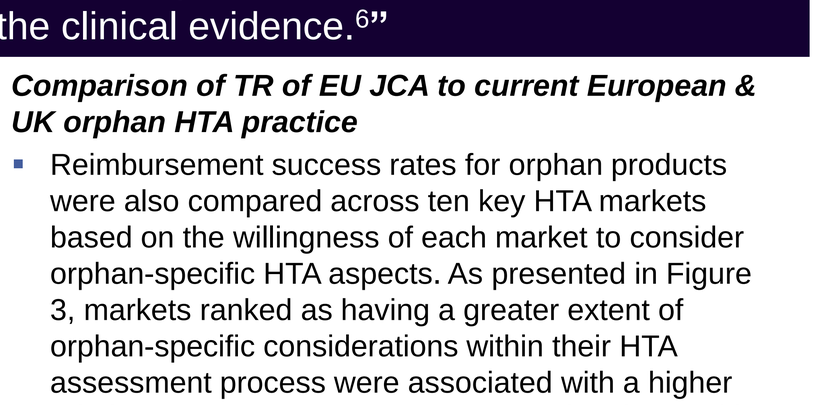
Figure 2: Reimbursement success rates for orphan products assessed through orphan-specific and standard HTA processes



Comparison of TR of EU JCA to current European & UK orphan HTA practice

- Reimbursement success rates for orphan products were also compared across ten key HTA markets based on the willingness of each market to consider orphan-specific HTA aspects. As presented in Figure 3, markets ranked as having a greater extent of orphan-specific considerations within their HTA assessment process were associated with a higher reimbursement success rate compared to those with fewer considerations for orphan products.
- Severity modifiers and more orphan criteria correlate with a greater likelihood of successful reimbursement (Figure 3); however, the EU JCA guidelines do not use any severity modifiers and do not make any special allowances for orphan products. Thus, will likely negatively affect reimbursement for orphan products.

Figure 3: Reimbursement success rates for orphan products based on extent of orphan-specific considerations in HTA processes



CONCLUSIONS

- Rare disease-specific HTA considerations acknowledge the challenges in evidence generation and are a key part of developing a fair HTA process that supports equitable access to treatments.
- Analyses suggest that more orphan-specific HTA considerations correlate with higher reimbursement rates.
- More work needs to be done by the European Commission and EU JCA subgroups to ensure that the upcoming EU JCA process will provide a fair assessment of the benefits of orphan products and avoid negatively affecting access for patients with rare diseases.

References

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initiateconsultancy.com *hello@initiateconsultancy.com*