AN EU HTA FIT FOR RARE DISEASES

Part 1: Clinical evidence in joint clinical assessments

Copenhagen Economics

European Expert Group on Orphan Drug Incentives
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European Expert Group on OD Incentives

Established in 2020, the European Expert Group on Orphan Drug Incentives (OD Expert Group) brings together representatives of the broad rare disease community, including researchers, academia, patient representatives, members of the investor community, rare disease companies and trade associations.

The group aims to become the source of ground-breaking ideas and potential solutions that will provide input to the Orphan Medical Products (OMP) Regulation evaluation. The initiative is led by a steering group composed of the European Organisation for Rare Diseases (EURORDIS), the Voice of Rare Disease Patients in Europe, and the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), representing several companies focused on finding new therapies for rare diseases.

The group is co-chaired by Professor Maurizio Scarpa, Coordinator of the European Reference Network for Hereditary Metabolic Disorders (MetabERN). The following EUCOPE member companies sponsor and provide expertise to the initiative: Alexion, Biogen, Bristol Myers Squibb, Chiesi, Novo Nordisk, PTC Therapeutics, and Takeda.

Source: https://od-expertgroup.eu

The OD Expert Group worked together with Copenhagen Economics in a series of workshops and interviews to investigate how the current framework for EU health technology assessment (HTA) needs to be adjusted to fit the needs of orphan medicines.
In this report, the OD Expert Group makes a set of recommendations that will improve the upcoming EU HTA for the needs of orphan development and will allow handling stakeholder involvement in joint clinical assessments (JCA) concerning conflicts of interest.

This is the third report produced by the OD Expert Group since 2020. The group's further work includes

- Orphan Medicine Incentives. How to address the unmet needs of rare disease patients by transforming the European OMP landscape – Link
- An operational framework for the modulation of orphan medicine incentives – Link

List of main acronyms

ACT	Appropriate Comparator Treatment
ATMP	Advanced Therapy Medicinal Product
CE	Cost-effectiveness
CHMP	Committee for Medicinal Products for Human Use
EC	European Commission
EMA	European Medicines Agency
EHDS	European Health Data Space
ERN	European Reference Network
EU	European Union
EUCOPE	The European Confederation of Pharmaceutical Entrepreneurs
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
HCP	Health Care Professionals
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
IQWiG / G-BA	Institute for Quality and Efficiency in Health Care / Gemeinsamer Bundesausschuss (Germany)

JCA	Joint Clinical Assessments
MA	Marketing Authorisation
MS	Member states
NHCI	National Health Care Institute (The Netherlands)
NICE	National Institute for Health and Care Excellence (UK)
ODD	Orphan Drug Designation
OMP	Orphan Medical Products
P&R	Pricing and reimbursement
QALY	Quality-Adjusted Life Years
RCT	Randomised controlled trial
RWD	Real-world data
RWE	Real-world evidence
SME	Small and medium-sized enterprise
R&D	Research and development
WTP	Willingness to pay

Glossary of key terminology in this report

Incentive	Any measure meant to promote the development of medicines to treat rare diseases
Indication	The labelled use of a specific drug (an OMP) for treating a particular disease
Marketing Authorisation (MA)	The approval to market a medicine in European Union member states
Orphan Drug Designation (ODD)	A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from specific incentives.
Real-world evidence (RWE)	Evidence on the usage and potential benefits or risks of a medical product derived from analysis of real-world data

EXECUTIVE SUMMARY

An EU HTA fit for rare diseases

1 Global standard data submission requirements impede access to OMP

Common diseases
Large patient populations

Rare diseases
Small, heterogeneous and geographically dispersed patient populations

Randomised controlled trials of high certainty feasible
Regarded as the gold standard, RCTs bring certainty about the effectiveness of the medicine at the market access stage.

Randomised controlled trials are not feasible, or results cannot be interpreted using traditional statistical significance thresholds due to e.g. small populations.

The European Union Health Technology Assessment (HTAR) Regulation[1] in recital 24 recognises the challenge and calls for adaptation.
"*Methodologies for performing joint clinical assessments and joint scientific consultations should be adapted to include specificities of new health technologies for which some data may not be readily available. This may be the case for, inter alia, orphan medicinal products (…).*"

2 Solution: EU HTA framework for rare diseases

Is gold standard data submission feasible?

Guidance A on feasibility sets criteria and clinical evidence requirements to separate OMP for which gold standard data submission is not feasible.

Yes

Gold standard data submission requirements

No

What should a feasible data dossier look like?

Guidance B on clinical evidence lays out what a feasible data dossier should look like, including evidence types, methodologies and significance thresholds.

The OD Expert Group incentives propose a framework that addresses the uncertainty in demonstrating clinical effectiveness for rare diseases. Developed together with HTA experts, the framework leads to optimal decisions on clinical effectiveness despite limited data for very rare diseases.

3 We call on the Coordination Group on Health Technology Assessment[2] to implement the framework to ensure efficient, fast and broad patient access to medicines for rare diseases.

1/ Regulation (EU) 2021/2282 on Health Technology Assessment [link]; 2/ The EU Regulation (EU) 2021/2282 has set up the Coordination Group on Health Technology Assessment. This group is made up of representatives from the member states. One of the main responsibilities of the Coordination Group is to develop guidance documents on methods and procedures. As stated in Article 4(1) of the Regulation (EU) 2021/2282, the Coordination Group is required to take into account the unique characteristics of health technologies, including those related to orphan medicinal products.

Executive summary

Market access is recognised as an important challenge.
Today, rare disease patients across EU member states experience delayed or lack of access to approved OMP.

Part of the access issue for OMP resides in the fact that HTA processes across EU member states are broadly not adapted to handle the uncertainty around the clinical effectiveness of OMP that can be demonstrated based on the available clinical evidence at the point in time of the assessment. This uncertainty results from the difficulty in conducting clinical research for small, heterogeneous and geographically dispersed patient populations, challenging the feasibility, design, and successful conclusion of clinical trials.

Typical challenges that OMP developers face when going through HTA assessments relate to the lack of acceptance of non-randomised and single-arm studies, the consideration of surrogate endpoints as lowering the quality of clinical evidence, the challenging choice of comparators and the lack of acceptance of RWE to fill evidentiary gaps in clinical trials.

The absence of an adapted HTA framework for rare diseases leads to suboptimal outcomes.
In extreme cases, failure at the HTA stage may ultimately prevent patient access by leading payers to decide against the reimbursement of the medicine. In less extreme cases, while not preventing a positive P&R decision, the lack of an adapted HTA framework may cause lengthier processes or sub-optimal decisions to be made by payers due to large perceived uncertainty.

Without transparent and similar guidelines across member states on how evaluations and eventually recommendations of new OMP will take place, the risk is great that data-gathering efforts may be duplicated to serve different needs across member states. Inequalities in access across member states may therefore persist or even be exacerbated over time. Conversely, a clinical assessment that can consider the specific challenges in the rare disease space will instead contribute to a decision-making process that appropriately reflects the value that OMP bring to rare disease patients.

The EU HTA Regulation calls for a tailored framework for rare diseases.
The recently adopted HTA Regulation[1] does not foresee any tailored framework for rare diseases. However, it recognises the need of adopting methodologies to reflect the specificities of OMP.

> **Methodologies for performing joint clinical assessments and joint scientific consultations should be adapted to include specificities of new health technologies for which some data may not be readily available. This may be the case for, inter alia, orphan medicinal products, vaccines and advanced therapy medicinal products** (Recital 24, the HTA Regulation)

The HTA Coordination Group will decide on such a framework
The HTA Regulation has set up the Coordination Group on Health Technology Assessment. This group is made up of representatives from the member states. One of the main responsibilities of this group is to develop guidance documents on methods and procedures. As stated in Article 4(1) of the HTA Regulation, the HTA Coordination Group is required to consider the unique characteristics of health technologies, including those related to OMP.

The European Expert Group on OD Incentives has identified a framework.
In a series of workshops and in collaboration with HTA experts, the European Expert Group on OD Incentives has identified an approach to such a formal framework. This report summarises the approach as a starting point for more technical implementation work.

1/ Regulation (EU) 2021/2282 on Health Technology Assessment [link]; 2/ ibidem.

Executive summary

A framework centred around detailed guidance documents

To put the above principles into practice, we propose a simple assessment framework centred around two steps and two detailed guidance documents; see the figure on the next page. The framework follows six key principles to constitute real progress in the assessment of OMP; see Box 1. It also recognises that developers should make maximum efforts to achieve the highest evidentiary standard possible.

In the first step, the HTA body considers whether the submission of an RCT-based dossier of high certainty yielding statistically significant results at conventional threshold level if the OMP is truly effective is achievable in the framework of a feasibility dialogue with the developer. The dialogue starts from a feasibility assessment conducted by the developer that explains why producing such a standard dossier is not possible or why conducting RCT is not the first-best option in this case. The assessment is supported by detailed guidance (**Guidance A**) setting out a comprehensive list of reasons that may make producing such a standard data dossier difficult, why this is relevant and what evidence must be provided to support this.

When the standard data dossier is not feasible, the developer moves on to Step 2. In Step 2, the HTA body and developer consider together what a feasible dossier based on complementary evidence should look like. If relevant, the resulting JCA should include an evidence generation plan for RWE that (i) is closely aligned with the plan required by the EMA at the regulatory stage, (ii) links up as much as possible to any future European infrastructure for collecting RWD, and (iii) provides detailed guidance for the optimal plan that should be accepted by the national HTA bodies, avoiding duplication.

This exercise is supported by detailed guidance (**Guidance B**) that sets out a comprehensive list of evidence types that can be produced and expectations for evidence levels, thresholds and applicable methodologies.

Two further mechanisms would make this two-step procedure as resource intensive as possible:

First, not all OMP must go through the fully-fledged feasibility dialogue. If a developer is confident that a standard data dossier is feasible, they can simply submit it. Second, foreseeing early and continuous dialogues or scientific advice between the developer, the HTA body and EMA allows prediction and adjustment of the data dossier needed in the assessment, helps plan evidence collection and trial designs accordingly, and increases the information flow or alignment with the regulatory stage.

The success of such a framework crucially hinges on the quality of the guidance documents. Drawing up this guidance, policymakers and technical experts should take inspiration from past HTA assessments across EU member states, some of which we outline in this report.

Appeal to change direction

At a time when the status of the debate seems to risk moving towards stricter requirements, the European Expert Group on OD Incentives calls for an HTA framework that can consider the specific challenges of the rare disease space.

Box 1. Six principles for a truly progressive framework

A flexible (not a prescriptive) framework

A comprehensive evidence principle

A pragmatic approach to managing uncertainty

The need for an EU-level RWE plan

The need for harmonised guidance on key methodological and evidentiary expectations

The involvement of stakeholders

The EU HTA framework for rare diseases

Overarching principle: HTA for rare diseases relies on the submission of comprehensive clinical evidence from different sources.

Early dialogue joint scientific consultation (JSC)

With reg + HTA pre-defining feasible data package

1 What types of clinical evidence can be generated for the JCA?

Can RCT data of high certainty be expected for all relevant patient populations?

Key input
JSC, scoping meeting with developer horizon-scanning input from patients and clinicians

Guidance A on feasibility
Key criteria that must be covered:
- Indicative prevalence thresholds
- Ethical and pragmatic issues of RCT, including the prevalence of the paediatric population

The outcome at the regulatory stage (conditional MA/exceptional MA) carries weight. No feasibility assessment is necessary for MA under exceptional circumstances, e.g., conditional MA.

2 What methods of interpretation should be applied?

Which alternative trial designs and complementary clinical evidence should be considered to complete the data picture?

Key input
JSC and scoping meeting with the developer
Patient and clinician perspectives, methodologically adequate collection of patient experience and ethnographic data
plan for further evidence collection (RWE)

Guidance B on clinical evidence

Single-arm trials vs pre-agreed threshold

- Outcomes of interest (patient-relevant/final/surrogate)
- Pre-agreed comparators, e.g., historical cohorts
- Direct or indirect comparisons, sophisticated statistical methods and other threshold values
- Role of additional data sources, e.g., RWE

1
The Challenge

2
The Opportunity

3
The Solution

1
THE CHALLENGE

Appraising medicines for rare diseases in HTAs

Market access is recognised as an important challenge for OMP. Today, rare disease patients across EU member states experience delayed or lack of access to approved OMP.

While the roots of access issues for OMP, and medicines more broadly, are multi-factored, part of the access challenge for OMP resides in the fact that standard market access pathways across EU member states are broadly not adapted to the characteristics and challenges of OMP, and medicines for rare diseases more broadly, despite some advances in individual member states in recent years.

Along the OMP development and market access pathway, OMP face two overall challenges:

- The first challenge relates to the **uncertainty as to the clinical effectiveness** that can be demonstrated based on the available evidence. This uncertainty results from the small, heterogeneous and geographically-dispersed patient populations, which complicates the conduct of research in clinical settings and challenges the feasibility, design, and successful completion of clinical trials. It also results from a lack of knowledge and information both on the natural history of many rare diseases and the direct and indirect disease burden.
- The second challenge relates to OMP generally having a **higher price per patient** than high-volume diseases, due to multiple failures and significant R&D investment in a small number of patients, which, in combination with the above-mentioned uncertainties, lead to cost-effectiveness estimates beyond standard WTP thresholds. In other words, putting a value on a treatment with uncertain effectiveness data is a complex and multifaceted challenge.

The challenges related to demonstrating clinical effectiveness today are recognised at the regulatory approval stage, where policymakers have explicitly provided for regulatory pathways that allow faster approval and patient access based on the available clinical data at a time where large anticipated benefits may outweigh the risks, e.g., in case of gene therapies, or when the nature of the condition may set natural limits to the data that can be collected in a narrowly defined clinical setting, e.g., for rare diseases. These include conditional MA or MA under exceptional circumstances or accelerated assessments. However, while an anticipated positive benefit-risk balance may be sufficient for granting marketing authorisation, the actual magnitude of the benefit will then need to be quantified to satisfy member states' requirements for the HTA and the P&R stage.

In HTA, where EU member states must assess whether a given treatment works better, equally well, or worse than existing alternatives, OMP face specific challenges that HTA processes across member states are often not designed to meet.

To accommodate small patient populations and ethical considerations, the trial design often involves non-RCTs, such as non-randomised and single-arm studies. However, since RCTs are the gold standard for the collection of clinical evidence, HTA bodies may be reluctant to accept data generated outside of RCTs. While the regulatory approval stage foresees specific pathways to accommodate such issues, i.e., conditional MA or MA under exceptional circumstances, the same pathways are not available at the subsequent HTA stage, posing a barrier to patients' access.

Even where RCTs may be feasible, reaching results with the required statistical significance is a challenge in a setting where the disease is rare, where patients are located in widely different geographic areas or are difficult to identify due to the lack of appropriate pathways for diagnosis. While various statistical methods exist to deal with these situations[1], there are no clear guidelines on which methods are accepted by HTA bodies, and HTA bodies often lack the skills to implement such methods.

The case of surrogate endpoints that enable clinical trials of smaller sample sizes and shorter durations is an example that proves particularly useful in the rare disease space. The use of surrogate endpoints is increasingly common at the regulatory approval stage, leading to earlier approval of life-saving treatments for patients. However, HTA bodies often do not agree on a common level of their validation, ultimately rejecting or recommending restricted access for OMPs that use surrogate endpoints.[2,3]

The choice of comparators is especially challenging as the standard of care often differs among EU member states and might correspond to an off-label treatment, which is often the case in the rare diseases space. In addition, the standard of care may not be another pharmaceutical but could be a device, a surgical procedure or, in many cases, best supportive care. This creates the need for clearer guidance and dialogue around the selection of appropriate comparators. This is a crucial issue at the HTA stage, where the comparative nature of the assessment is stronger.

The described limitations in generating adequate clinical data at the time of the HTA decision create a need to gather more RWD that may take several months or years to generate. However, RWE to fill evidentiary gaps in clinical trial data is also not routinely accepted, at least not to the extent that the EMA does at the regulatory stage, due to the lack of protocols for RWD generation and use of RWE at the MS level. Moreover, the additional data needs for a final P&R decision are currently identified by each national HTA body, thus creating further room for heterogeneity and duplicative efforts.

This shows that due to its nature, the rare disease space presents specific challenges that increase the uncertainty faced at the HTA stage. While pragmatic approaches have been adopted for regulatory approval, this is often not the case for the HTA stages, which creates further uncertainties and hurdles for developers. The result is a need for processes and procedures that manage this uncertainty and, if the uncertainty cannot be managed away, a standard for taking decisions under intrinsically more uncertain circumstances.

Sources: 1) See alternative statistical methods such as Asterix, IDEAL, and Bayesian statistics; 2) Ciani et al. (2021): "Validity of Surrogate Endpoints and Their Impact on Coverage Recommendations: A Retrospective Analysis across International Health Technology Assessment Agencies, Link; 3) FTI Consulting (2021): "Challenges in Preserving Access to OMPs Under an HTA Framework", Link.

2
THE OPPORTUNITY

Adjusting EU HTA to the needs of rare disease medicines development

The new EU Health Technology Assessment (HTA) Regulation[1] (Regulation 2021/2282 on health technology assessment), which came into force in January 2022, regulates a common EU-level HTA for innovative therapies. In particular, the HTA Regulation creates the legal and organisational framework for cooperation between EU member states in JCA of new therapies and JSC.[2]

The goals the HTA Regulation aims to achieve through EU-level cooperation are:

- to speed up patients' access to new therapies,
- to reduce the duplication of work linked to parallel national-level processes for HTA,
- to improve predictability for companies on the processes and outcomes of clinical assessment,
- and to strengthen the quality of HTA across member states.[2]

The EU HTA Regulation establishes that a member state coordination group composed of representatives from national HTA bodies will oversee the JCA of new therapies.

Importantly, the cooperation will only include the clinical assessment of the HTA, i.e., the estimation of relative clinical effectiveness and safety of health technologies compared to existing ones, since "*in principle this is the component that is more generalisable from setting to setting*".[3] Any cost-effectiveness assessment, value assessment, and following P&R decisions will remain in the domain of the member states. In other words, important decisions that impact the assessment of the relative value of the health technology will be made at the EU level, including the choice of comparator, endpoints and overall acceptance of the data provided.[4]

While the JCA was originally intended to replace national assessments concerning the clinical part of the HTA, the JCA report is not legally binding for member states. This means that national HTA bodies retain a level of discretion and could diverge from the JCA report, i.e., they can conduct additional assessments and can ask for further data, new evidence and new comparators. In addition to the JCA, the HTA Regulation provides the possibility for developers to request a JSC on clinical trial design, choice of comparator, endpoints, interventions, health outcomes and patient populations.

In principle, the EU HTA Regulation could lead to more efficient HTA across the EU because it allows member states to pool resources and expertise while avoiding duplicative efforts and developers to benefit from greater predictability and efficiency when only one EU-level submission is required.[3] Other stakeholders, such as patients and clinicians, will also benefit if a new transparent assessment framework facilitates input and allows addressing inequalities across countries.

However, in practice, the potential for greater efficiency may not be fully exploited. The fact that the JCA is not legally binding leads to a risk of duplication of the work by national HTA bodies, depending on their degree of acceptance of the applied approaches and methodologies in the JCA. Moreover, the limited capacity for JSC means that not all developers will be able to obtain scientific advice.

The HTA Regulation will be implemented as of 2025 for oncology products and ATMPs, to OMP from 2028, and from 2030 to the remainder of medicines approved under the EU centralised procedure.

In the coming two years preceding the implementation of the HTA Regulation, the underlying processes and methods for the EU HTA will be fleshed out. How these methodologies and approaches look will have a great impact on patients' access to medicines, especially how fast patients can access medicines.

The EU HTA Regulation calls for specific methodologies for rare diseases

Today, the specific challenges to developers in the rare disease space across the development path, including at the HTA stage, are widely recognised and documented. Despite this, the EU HTA Regulation does not foresee any tailored framework for assessing OMP, or medicines for rare diseases more broadly. In the recitals, however, the policymakers recognise the need of adopting methodologies to reflect the specificities of orphan medicinal products.[5]

The lack of an adapted pathway for OMP at the HTA stage would lead to suboptimal outcomes for OMP access and therefore rare disease patients. In extreme cases, failure at the HTA stage may ultimately prevent patients' access by leading payers to decide against the reimbursement of the OMP. In less extreme cases, while not preventing a positive P&R decision, lack of adapted HTA may cause lengthier processes or sub-optimal decisions by payers due to large perceived uncertainty. Conversely, a clinical assessment that can consider the specific challenges of OMP will instead contribute to a decision-making process that appropriately reflects the value that OMP bring to rare disease patients.

Conversely, without transparent and similar guidelines across member states for how evaluations and eventually recommendations of new OMP will take place, the risk is great that data-gathering efforts may be duplicated to serve different needs across member states and that inequalities in access to OMP across member states will persist or even be exacerbated over time.

Methodologies for performing joint clinical assessments and joint scientific consultations should be adapted to include specificities of new health technologies for which some data may not be readily available. This may be the case for, inter alia, orphan medicinal products, vaccines and advanced therapy medicinal products.

HTA Regulation, Recital 24

The implementation of the EU HTA regulation is an opportunity for an improved framework.

The implementation phase of the regulation is an opportunity to create an adapted guidance framework for OMP. The HTA Regulation has set up the Coordination Group on HTA. One of the main responsibilities of this group is to develop guidance documents on methods and procedures. It will do so by considering the unique characteristics of OMP.[6]

Sources: 1) Regulation (EU) 2021/2282 on Health Technology Assessment Link; 2) ibidem; 3) Drummond et al. (2022): "European union regulation of health technology assessment: what is required for it to succeed?", Link; 4) Regulation on Health Technology Assessment, recital 14; 5) Regulation on Health Technology Assessment, recital 24. 6) Regulation on Health Technology Assessment, Article 4(1).

An adapted HTA approach for rare diseases is a crucial step for efficient, fast and broad patient access.

Adapted EU HTA is necessary for efficient, broad and fast patient access to medicines for rare diseases.
An EU HTA approach adapted to the challenges of OMP is a further step to shaping an overall pathway for OMP that accounts for rare disease-specific challenges; see Figure 1. The EU has made considerable efforts to ensure that more therapies are made available to rare disease patients, with the OMP Regulation, ERNs, and the exceptional circumstances pathway for regulatory approval. An adapted pathway for OMP at the HTA stage would support this overall goal. In that sense, it is a crucial step to ensuring efficient, fast and broad patient access across the EU.

Firstly, it can lead to greater clarity on evidentiary expectations for the developer, a better and more comprehensive data picture to support clinical effectiveness in line with patient and clinician perspectives, and clear plans for handling remaining evidentiary uncertainties. On that basis, it can generate solid input for clinical and value assessments in national HTA processes and P&R decisions. Ultimately, high-quality HTA for OMP may increase the likelihood of positive HTA and reimbursement decisions for OMP and improve the speed of decision-making. This is corroborated by data across EU member states[1], which shows that countries where special HTA criteria for OMP existed in 2016 had a high rate of positive HTA recommendations; see Figure 2 on the next page.

Figure 1. Challenges and solutions for OMP along the regulatory and market access pathway

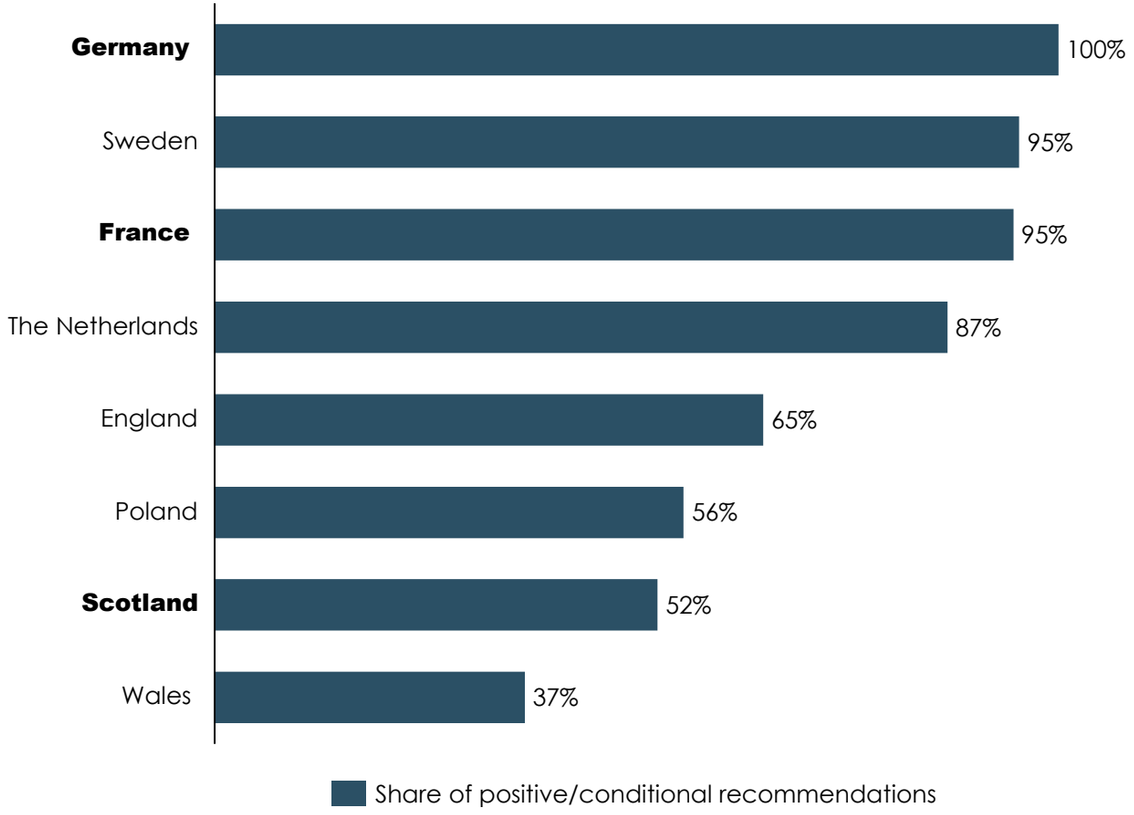
		Health Technology Assessment		
Step	**Regulatory approval**	**Clinical assessment**	**Economic assessment**	**P&R decisions**
What happens	The authority evaluates the safety and efficacy of a given product. A positive benefit-risk balance is grounds for regulatory approval.	The authority evaluates the relative efficacy of a given product compared to the standard of care.	The authority assesses relative cost-effectiveness.	Reimbursement and price are decided.
OMP challenges	Small patient populations and poor knowledge of disease history lead to a lower degree of evidentiary basis for assessment.	Small patient populations and poor knowledge of disease history lead to a lower degree of evidentiary basis for assessment.	Assessing value in the face of uncertainty is difficult. Often no specific WTP thresholds or budgetary considerations are applied to orphans.	High per-patient price in the face of uncertain effectiveness at the point of the P&R decisions.
Types of solutions	Where necessary, accept alternative types of evidence and further data gathering requirements, e.g., MA under exceptional circumstances and conditional MA.	Where necessary, accept alternative types of evidence and alternative methods of interpretation coupled with further data gathering requirements to dimmish uncertainty in the future.	Adjusted WTP thresholds and overall budgetary versus per-patient cost considerations.	Managed entry agreements and other flexible payment models.
Level	**EU**	**Ideally EU-level with limited MS specificity**	**Member states[2]**	**Member states**

Sources: 1) Kawalec et al. (2016): "The correlation between HTA recommendations and reimbursement status of OMPs in Europe", Link 2) The EU HTA Regulation includes provisions for voluntary cooperation in non-clinical assessment (see Section 4, article 23).

An adapted HTA approach for rare diseases is a crucial step for efficient, fast and broad patient access.

Figure 2. Correlation between special orphan HTA criteria and positive recommendations of OMP

Shares of recommendations for OMP
Countries with special HTA criteria for OMPs in 2016 in bold



Conversely, the absence of an adapted pathway for OMP at the HTA stage can lead to suboptimal outcomes for OMP access and therefore rare disease patients. In extreme cases, failure at the HTA stage may ultimately prevent patients' access by leading payers to decide against the reimbursement of the OMP. In less extreme cases, lack of adapted HTA, while not preventing a positive P&R decision, may cause lengthier processes or sub-optimal decisions by payers due to large perceived uncertainty.

In fact, while clinical assessment is only one step on the access pathway, these considerations are reflected in the availability of OMP across EU countries. For instance, Germany and France, with special HTA criteria for OMP, have high rates of availability of approved OMP, 90% and 79% respectively.[2]

Secondly, high-quality output at the EU HTA stage can counter the risks of duplicative efforts by HTA bodies in member states by improving the trust and acceptance of the assessment already conducted. Avoiding duplication is key in a context where both national HTA bodies and (often small) companies are resource-constrained. In other words, a JCA that is as relevant as possible to all member states will lead to greater resource efficiency for all stakeholders.

Adapted EU HTA is not a sufficient condition for fast and broad patient access.
Adapted EU HTA alone will not pave the way for broader and faster patient access as it is still limited to the evaluation of clinical effectiveness. Even with a perfect EU-level JCA acknowledged by all HTA bodies in the member states, broad and fast patient access is still reliant on the economic assessment in each member state, which involved value considerations including WTP thresholds and budget-impact considerations. For OMP access to function properly, national HTA bodies and health authorities need to adapt their ways of handling evidentiary uncertainty in value assessments, for instance by adjusting WTP thresholds, by introducing decision mechanisms that consider budget impact or by implementing managed entry agreements. These steps merit further attention.

Note: Kawalec et al. (2016) identify 101 EMA-authorised OMP in a time frame from 1 Nov. 2002 to 30 Sep. 2015. Shares are based on the number of drugs actually assessed by each HTA agency, which varies from 20 for England to 75 for France.

Sources: 1) Kawalec et al. (2016): "The correlation between HTA recommendations and reimbursement status of OMPs in Europe", Link ; 2) IQVIA (2023) EFPIA Patients W.A.I.T. Indicator 2022 Survey, page 27 Link

Across the EU, pragmatic approaches to assessing OMP already exist.

Across the EU, pragmatic HTA approaches to assessing OMP are rather common. At least six member states either have separate pathways or apply special considerations to specific types of OMP as part of the overall appraisal. See the overview in Table 1 and more detailed examples in the box on the following page. In other member states, we might see a gap between theory and practice, where the evidentiary standards for HTA are overall high but practical solutions are found in the assessment of OMP that cannot abide by these standards.

In fact, a study assessing HTA processes in 32 countries [7] concluded that 78% of these countries deal with OMP differently: 41% have supplemental processes, 31% have standard processes but use other special features facilitating appraisal of OMP, and 6% have appraisal criteria likely to favour OMPs[7]

Hence, an adapted HTA approach to OMP at the EU level would cast already-existing practices into a formal framework.

Table 1. HTA approaches to orphan medicine assessment[1,4]

Member State	HTA Approach to OMPs
Germany	• Lower levels of statistical significance are accepted for designated OMP • If validated, surrogate endpoints are considered acceptable to assess clinical effectiveness • Additional benefit is considered proven at MA if the budget impact is less than €30 million per year for a particular indication • Higher therapeutic benefit is automatically recognised for OMP
France	• Additional benefit is considered proven at MA if the budget impact is less than €30 million per year for a particular indication • If validated, surrogate endpoints are considered acceptable to assess clinical effectiveness • An accelerated HTA procedure is available for all innovative drugs, not only for OMP • Historical controls may serve as comparators if no active treatment alternative exists • The Agency for the Sanitary Security of Health Products can issue authorisations for temporary use in the case of life-threatening conditions or/and when there is no therapeutic alternative; this is not specific to OMP but can be applied to them • Early access programmes that can support the generation of early RWE
Scotland	• Alternative types of evidence are accepted for clinical trials, e.g., on efficacy and safety, and in economic evaluations • Additional data may be required, e.g., surrogate markers and quality-of-life data • Ultra-orphan medicines pathway facilities conditional market introduction to collect evidence on effectiveness
Sweden	• If validated, surrogate endpoints are considered acceptable to assess clinical effectiveness • Historical controls may serve as comparators if no active treatment alternative exists • OMP require no budget impact analysis • Cost-effectiveness thresholds are more lenient for drugs that address a high need[5] • Decision modifiers for the severity of a disease[6]
Lithuania	• OMP for ultra-rare diseases do not have to prove cost-effectiveness to be included on the reimbursement list[3]
The Netherlands	• Additional benefit is considered proven at MA if the budget impact is less than €2.5 million per year for a particular indication[2] • Conditional inclusion in basic health care can be applied for before HTA or after a negative assessment due to insufficient evidence • Decision modifiers for the severity of a disease[6]

Sources: 1) Stafinski et al. (2022): "HTA decision-making for drugs for rare diseases: comparison of processes across countries", Link; 2) Czech et al. (2020): "A review of rare disease policies and OMP reimbursement systems in 12 Eurasian countries", Link; 3) Malinowski et al. (2020): "Health technology assessment and reimbursement policy for oncology OMPs in Central and Eastern Europe", Link; 4) Kawalec et al. (2016): "The correlation between HTA recommendations and reimbursement status of OMPs in Europe", Link; 5) Ollendorf et al. (2018): "Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers", Link; 6) Lee et al. (2022): "The Challenge for OMPs Remains: Three Case Studies Demonstrating the Impact of Changes to NICE Methods and Processes and Alternative Mechanisms to Value Orphan Products", Link ; 7) EEA countries plus Australia, Canada and New Zealand. Nicod et al (2020): Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches. Link.

Across the EU, many initiatives can be built on.

England: NICE[1]

NICE has established a highly-specialised technology programme (HST) to evaluate specific medicines in the context of very rare conditions. Around three of these ultra-OMP are selected by the Department of Health to undergo HST each year via a prioritisation process.[7]

However, many OMP do not meet the strict eligibility criteria of HSTs and are hence evaluated in standard single (STA) or multiple technology (MTA) appraisals.

The decision-making process of NICE relies on a clearly specified cost-benefit assessment, which uses incremental quality-adjusted life years (QALYs) to compute tangible cost-benefit thresholds (ICERs).

Decision modifiers may increase the weight of QALYs provided by a treatment if either the expected health benefits are very large or the treatment addresses a very severe disease. Additionally, a managed access agreement may provide innovative treatments with a conditional market inclusion to generate RWE and address previous uncertainties.

For STAs or MTAs, the ICER upper boundary is £20,000 to £30,000. For HSTs, this boundary is £100,000. The share of OMP recommended through the STA/MTA is identical to that of non-OMP, suggesting that some leniency is de facto granted to the evidence of OMP.[9]

Germany: IQWiG / G-BA

OMP that are classified as such according to EU Regulation (EC) Nr. 141/2000 are assumed to have proven additional health benefits. A regular benefit assessment is only conducted once the drug exceeds an annual revenue threshold of €50 million.[2]

The regular benefit assessment at IQWiG[3] includes a classification of the evidence provided, which follows the G-BA rules[2], and a grade of recommendation system, which approaches the recommendation system outlined by the "Nationale Versorgungs Leitlinien"[4] (NVL).

Generally, the evidence standard provides the baseline for a grade of recommendation. The highest level of evidence is assigned if the findings are based on at least one RCT. However, the final grade of recommendation may also include patient preferences and ethical concerns, which may result in a decision that deviates from the results of the pure assessment of the level of evidence.

The Netherlands: NHCI[5]

Most drugs that have been authorised by EMA are automatically included in the basic health care package in the Netherlands. A formal HTA assessment is usually not conducted for OMP if the budget impact is less than €2.5 million per year.[8]

NHCI has created a conditional inclusion policy that aims at addressing the challenges of generating sufficient evidence to prove effectiveness in the case of OMP, among others.

This policy allows manufacturers to collect clinical evidence for up to seven years, or in special cases up to 14 years, before the drug is reviewed by the NHCI. The review is based on NHCI´s "established medical science and medical practice", which outlines the quality of evidence classification and important factors in its cost-benefit decision.[6]

Drugs are eligible if they address an unmet medical need according to the EMA definition. This states that no satisfactory method of diagnosis, prevention or treatment for the respective condition exists in the EU or that the treatment under consideration provides significant advantages.

Once included in the policy, NCHI and the manufacturer agree on a market price for the duration of conditional inclusion, which is made public. Also, all participating parties set up a joint covenant containing guidelines that the coming research aims to fulfil.

Sources: 1) NICE (2022): "NICE health technology evaluations: the manual", Link; 2) G-BA (2022): "Verfahrensordnung des Gemeinsamen Bundesauschusses", Link; 3) IQWIQ (2022): "General Methods", p. 117-118, Link; 4) Nationale Versorgungs Leitlinien (2017): "Methodenreport", Link; 5) NHCI: "Conditional inclusion of OMPs, conditionals and exceptionals in basic health care", Link; 6) NHCI (2015): "Assessment of 'established medical science and medical practice'", Link; 7) NICE – Highly specialised technologies guidance, Link ; 8) Czech et al. (2020): "A Review of Rare Disease Policies and OMP Reimbursement Systems in 12 Eurasian Countries", Link; 9) Clarke et al. (2021): "The impact of rarity in NICE's health technology appraisals", Link;

3
THE SOLUTION

An adapted EU HTA framework for rare diseases: key principles

To be widely adopted, an adapted EU HTA framework for rare diseases should follow a number of key principles:	
A flexible (not a prescriptive) framework	The differing nature of rare disease treatments is such that we need a flexible framework to assess the treatments, allowing reflection on their individual challenges. Setting up unsuitable rules, for example on evidentiary requirements, is therefore not helpful. Instead, what we need is a framework that is predictable for all stakeholders involved and allows for alternative methods of interpreting the available data.
A comprehensive evidence principle	Instead of judging OMP only on the RCT gold standard, orphan HTA assessment should start from a principle of "comprehensive evidence", whereby all relevant evidence must be provided and evidence produced outside the context of randomised controlled trials (i.e., single-arm trials) must be accepted. This includes RWE with early data from compassionate-use programmes and further evidence collection to fill evidence gaps.
A pragmatic approach to managing uncertainty	Given the available evidence, for most orphans, HTA bodies will need to accept higher levels of evidentiary uncertainty at the time of HTA than for non-orphans and show larger tolerance in the assessment of the evidence provided, recognising the inherent limitations for generating data. The plan should be to decrease uncertainty following market access, e.g., through the collection of RWE.
The need for an EU-level RWE plan	A plan for the collection of RWE following market access should be developed at the EU HTA level. The plan should not trigger further requirements or separate discordant plans at the national level.
The need for harmonised guidance on key methodological and evidentiary expectations	EU-level HTA needs to provide harmonised EU-wide guidance on any alternative methodologies to apply or expectations for evidence in the orphan context, including the underlying reasoning. Such guidance will ultimately form the building block for new standards to assess orphans across Europe. It will provide for more homogeneity across European HTA assessments as well as the least possible duplication between EU- and national-level HTA.
The involvement of stakeholders	To ensure predictability, the procedure should involve maximum opportunities for dialogues between the developer, HTA and EMA and other stakeholders to align expectations on the relevant data and methodologies for the assessment. This should include early dialogue, i.e., JSC, and interactions throughout the assessment, i.e., the scoping process and finalisation of the draft JCA report. It will require an appropriate resourcing and funding mechanism.

An adapted EU HTA framework for rare diseases: the framework

As a guiding framework for an HTA for orphans, we propose a **framework for the development of further guidance for JCT of OMP; see Figure 3 on the next page**. This framework builds on the premise that all relevant evidence needs to be submitted and will be considered. It also recognises that developers should make maximum efforts to achieve as high an evidentiary standard as possible and that the specific circumstances of a given rare disease may mean that the gold standard of RCT data is not always attainable. As a result, a more varied data package needs to serve as a basis for the assessment.

The **first consideration** in the assessment is early dialogue to align the evidence that can be generated through clinical studies, whether through RCTs or single-arm trials.

We propose developing further guidance (**Guidance A**) setting out a comprehensive list of reasons that may make producing a standard data package difficult, why this is relevant and what clinical evidence must be shown in support. These could be, for instance, the impossibility to conduct an RCT. It could also be that the possible RCT does not allow sufficient coverage of different patient populations. We describe Guidance A in more detail on pages 11 and 12. Importantly, the submission of the developer should also consider key insights produced at the regulatory stage.

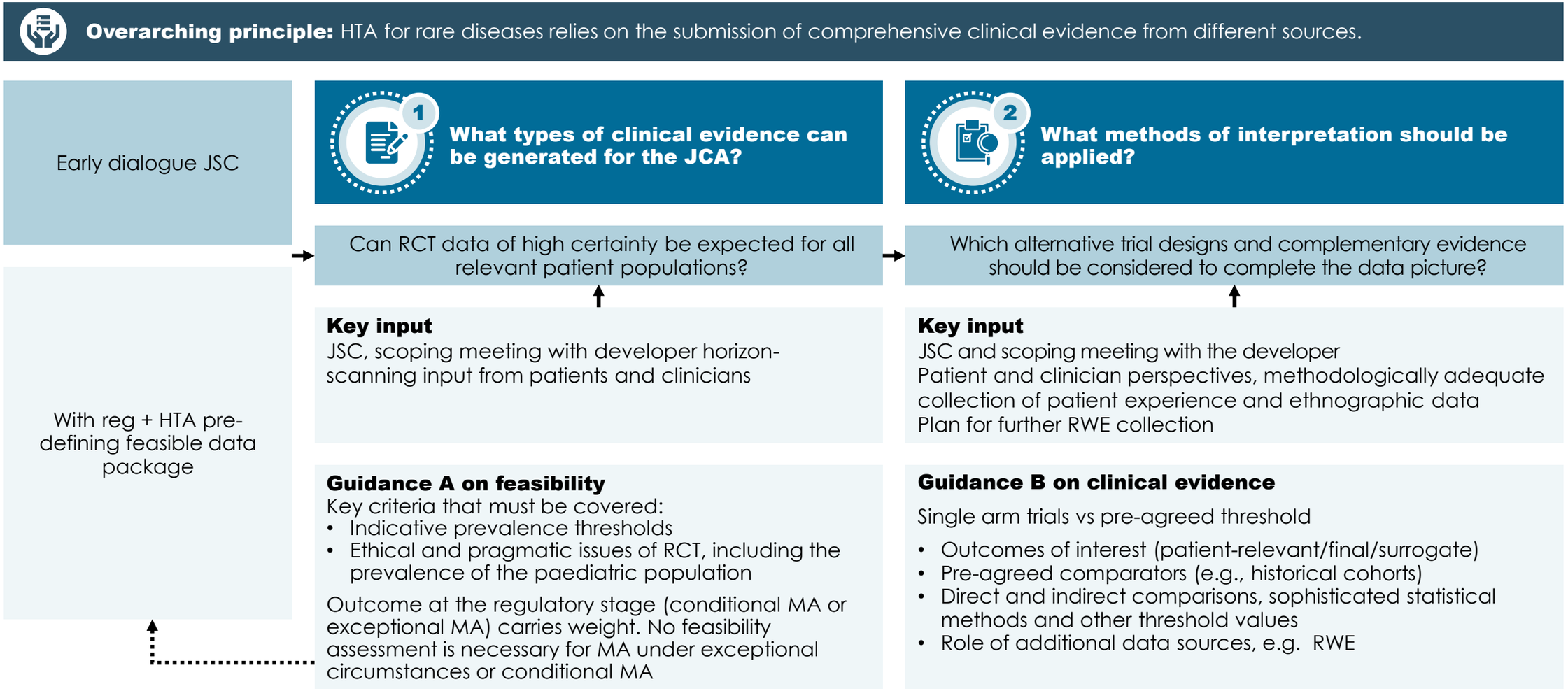
When the feasibility of the evidence collection is not given, the second consideration is what should be part of a data package based on complementary evidence. Importantly, this needs to closely involve all stakeholders, including developers, patients' and clinicians' perspectives in guiding the discussion on the most relevant evidence and endpoints. If relevant, the resulting JCA should include an evidence generation plan for RWE that (i) is closely aligned with the plan required by EMA at the regulatory stage, (ii) links up as much as possible to any future European infrastructure for collecting RWD, such as EHDS and Darwin EU, and (iii) provides strong guidance for the optimal plan that should be accepted by the national HTA body, thus avoiding duplication.

We also propose to develop detailed guidance (**Guidance B**) setting out a comprehensive list of clinical evidence types that can be produced and expectations for evidence levels, threshold and applicable methodologies to ultimately arrive at a harmonised approach to assessing OMPs in JCA, and prevent delays in access for patients.

We emphasise the importance of **early and continuous dialogue** and **scientific advice** between the developer, the HTA body and EMA to allow prediction and adjustment of the data package that will be needed in the assessment, help plan evidence collection and trial designs accordingly, and increase the information flow and alignment with the regulatory stage.

An adapted EU HTA framework for rare diseases: the framework

Figure 3. Overview of the proposed EU HTA framework



Guidance A: What may hinder the provision of an RCT-based data dossier?

The goal of Guidance A is to support an informed, case-by-case dialogue between the developer and the HTA body on what evidence can be generated based on the specific circumstances at hand. The guidance should feature a comprehensive list of reasons that producing RCT data may be difficult or not feasible, depending on the features of the disease and treatment.

Having such a high-quality dialogue will increase trust between the HTA body and the developer and allow alignment on alternative methods of interpretation, additional evidence to be generated and the overall parameters for the assessment, based on member states' needs.

The challenges that may make RCT difficult or impossible to conduct may be included in such guidance; see the overview in Table 2. The EUnetHTA 21 provides practical guidance on some of these challenges, such as how to deal in practice with direct and indirect comparisons,[1] methodological guidance regarding the validity of non-RCT studies,[2] and how to deal with several issues encountered around the assessment of endpoints.[3] Additional challenges may arise from ethical concerns. The situations we describe here and on the following page are a non-exhaustive list of examples, whereas the guidance should be as comprehensive as possible.

Table 2. Overview of challenges to be addressed by Guidance A

Challenge	What the guidance should do
Low disease prevalence may make RCTs difficult from a statistical point of view.	• set out typical situations in which a low sample size driven by low disease prevalence hinders the conduct of RCT • provide recommendations on how to mitigate this issue
Ethical concerns may prevent RCT design.	• specify when ethical reasons are convincing enough to lower requirements on full placebo exposure • outline standard situations in which these ethical concerns may arise
Lack of knowledge about the natural history of a disease is a key obstacle to RCT design.	• account for the extra effort for the developer when a natural disease history is not yet well-established • provide advice on how to summarise knowledge about the disease and conduct an informing natural history study
The high relative prevalence of paediatric populations may make RCT design difficult (ethical concerns).	• provide information on how to adapt the measurement of certain clinical outcomes and incorporate additional safeguards for paediatric populations • clearly outline potential decision modifiers due to a high paediatric prevalence
Other pragmatic issues	• provide information about study recruitment and retention

Note: this is a non-exhaustive list

Sources: 1) EUnetHTA 21 deliverables D4.3; 2) EUnetHTA 21 deliverables D4.6; 3) EUnetHTA 21 deliverables D4.4; 4) Kruer MC, Steiner RD (2008): The role of evidence-based medicine and clinical trials in rare genetic disorders, link ; 5) Jemima E. Mellerio (2022): The challenges of clinical trials in rare diseases, link.

Guidance A: What may hinder the provision of an RCT-based data dossier?

Ethical concerns

Ethical concerns may prevent RCT design in a rare disease context. Standard placebo-controlled trials may involve patients being excluded from a treatment that otherwise would be expected to significantly slow down disease progression or improve quality of life.[1] However, excluding patients from the benefit of a treatment may not be ethical, especially when no other treatments are available to them.

For instance, Fureman et al. (2017)[2] analyse the possibility of modifying the RCT trial design due to ethical concerns, among others. As a motivation, they take the results from a meta-analysis of studies for a new antiepileptic drug. Patients in the control arm of these studies had either received a placebo or ineffective doses of the drug studied. Results from the meta-analysis showed a threefold to fivefold increase in the rate of sudden unexpected death in epilepsy for patients who had been randomised to the control arm.

The guidance must therefore specify when ethical reasons are convincing enough to lower requirements on full placebo or control group exposure. The guidance should therefore outline standard situations in which these ethical concerns may arise.

Lack of natural history knowledge

Lack of knowledge about the natural history of a disease is a key obstacle to RCT design. The natural history of a disease refers to the natural progression of a disease in an individual over time in the absence of treatment.

Rare diseases are often classified into several subpopulations, some of them barely studied. Observable characteristics of the disease (phenotypes) and symptoms may vary across subgroups and the standard of care may hence be very heterogenous across jurisdictions.[8] This lack of knowledge factors into several components of the trial design, e.g., comparators, patient inclusion criteria and dosing, and likely influences the level of uncertainty of the generated evidence.[1] The guidance must hence account for the extra effort that needs to be made by developers when a natural disease history is not yet well-established.

An elaborate natural history study can be crucial in these cases. It aims to understand the progression of a disease and collect evidence on population heterogeneity, patient and caregiver perspectives, and the status of the current standard of care. These studies are increasingly used to optimise clinical planning in rare diseases and provide the foundation for supporting single-arm trials with external controls.[3]

The guidance must therefore outline how to take advantage of existing natural history studies and how these may be effectively conducted by the developer.[1]

High prevalence of paediatric patients

A significant share of rare disease patients are children, but customised treatments for paediatric patients are still rare. Today, most treatments are developed for adults. Additional safeguards for paediatric patients may limit the use of some clinical trial procedures otherwise acceptable for adults.[1] On the other hand, some relevant clinical outcomes may not be measurable in certain paediatric populations.[4]

Additionally, adequate patient-reported outcome measures for paediatric populations are frequently lacking. Self-reporting is not generally possible in paediatric populations, so outcomes may depend on parents reporting or other proxies.[6]

The guidance must indicate how to address the difficulties in conducting trials and reporting outcomes in relation to paediatric populations.

Today, appraisal decision-makers tend to make more allowances for a treatment that addresses a condition that severely affects paediatric populations. However, HTA bodies generally do not officially state such modifications to standard decision-making.[4] For example, when NICE assessed Risdiplam for treating spinal muscular atrophy (SMA), they considered whether adjustments to its normal considerations were needed due to the high prevalence of paediatric SMA populations. Such adjustments involve a balance of "the importance of improving the lives of children and their families with fairness to people of all ages". Ultimately, NICE "acknowledged and considered the nature of the eligible population as part of its decision making."[5] The extent remains uncertain, however. A framework that systematically weighs all inputs, including paediatric considerations, may improve transparency and procedural fairness.[7]

Hence, the guidance must clearly outline potential decision modifiers that allow flexibility in the assessment of medicines that mostly target paediatric populations. These modifiers must then be coherently applied to all assessments where they are relevant.

Sources: 1) FDA (2019): "Rare Diseases: Common Issues in Drug Development: Guidance for Industry", Link; 2) Fureman et al. (2017): "Reducing placebo exposure in trials: Considerations from the Research Roundtable in Epilepsy", Link; 3) IQVIA (2020): "Natural History Studies for Rare Diseases", see EUnetHTA guidance document D4.3; Link; 4) impactHTA (2021): "Deliverable D10.1: HTA Appraisal Framework Suitable for Rare Disease Treatments (Orphan Medicinal Products)", Link; 5) NICE (2021): "Risdiplam for treating spinal muscular atrophy", Link; 6) EUnetHTA21 guidance document D4.4; 7) Ollendorf et al. (2018): "Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers", Link; 8) Nestler-Parr et al. (2018): "Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group", Link;

Guidance B: What are the evidentiary expectations in a non-RCT setting?

The goal of Guidance B is to guide the developer and HTA assessors on the type of complementary evidence a developer can be expected to present in different cases and the strengths and weaknesses of specific types of evidence. The goal of Guidance B is to help the developer and HTA body work with the available evidence to constitute a data package that is as comprehensive as possible at the time of HTA, to make it more transparent in the JCA why certain types of evidence have been used over others in order to inform national decision-making, and to determine which future data collection is still necessary to address remaining uncertainties.

Several key issues should be included in such guidance; see the overview in Table 3.

Alternative clinical trial designs and methods of interpretation (comprehensive review of available evidence)

Treatments for rare diseases must demonstrate substantial evidence of clinical benefit in adequate, well-controlled studies. In rare diseases, study populations are often small, so evidence is difficult to gather. When RCT is not possible, the alignment between the health technology developer and the HTA assessors is needed in three aspects.

First, a harmonised EU-wide approach is needed concerning which course of action is preferable under which conditions. In some situations, it might be advisable to conduct RCT even though the interpretation of results may be less clear or the RCT may be underpowered. In others, RCT may not be considered the first best choice.

Second, when RCTs are not feasible, the developer may turn to alternative clinical trial designs. In the past, alternative designs such as single-arm trials with external controls have been accepted by HTA bodies in the orphan context. See Box 1 on the next page. While the EUnetHTA21 guidance will allow for the same (include reference to guidance on indirect-direct comparisons, and validity of clinical studies), many of the methods described are not endorsed or not recommended, meaning that individual MS might choose to conclude that there is insufficient evidence to judge the added value of the technology. Therefore, the harmonisation of approaches, thresholds and acceptance by all MS of the same methods is needed so as not to impede patient access.

Table 3. Overview of key issues to be addressed by Guidance B

Key issue	What the guidance should do
Alternative clinical trial designs	• outline strengths and weaknesses of acceptable study designs other than RCTs in relation to a given disease context
Alternative evidence	• endorsement of alternative methods of interpretation that can be applied in JCA in conditions where the disease context requires it • elaborate what these conditions are
Selection of endpoints	• explain when the use of surrogate endpoints is a valid choice • agree on conditions for acceptance of surrogate endpoints in national procedures that have been validated and used for JCA
Choice of comparator	• develop guidance for the selection of appropriate comparators (based on existing EUnetHTA guidance 2015), which ranks preferences for comparators based on the pros and cons of the choice of different comparators • further specify acceptable methodological approaches for valid indirect treatment comparisons • outline how the European HTA should specify a list of care standards against which a given treatment should be assessed if the standard of care is heterogenous across countries, e.g., European treatment guidelines
New statistical methods	• provide a framework for how new statistical methods will be continuously assessed
Role of additional data sources, e.g., RWE	• specify when RWE is considered suitable to address specific uncertainties • provide a framework and methodology for the process of collecting RWE

Note: this is a non-exhaustive list

Sources: Copenhagen Economics

Guidance B: What are the evidentiary expectations in a non-RCT setting?

Clear guidance on acceptable study designs and methods of interpretation is needed for a predictable EU HTA for OMP. The guidance should therefore outline different study designs that deviate from RCTs and specify strengths and weaknesses in relation to a given disease context[2]. The following non-exhaustive list[1] of alternative trials designs should be covered:

- crossover and n-of-1 trials
- randomised placebo-phase design
- enriched enrolment
- randomised withdrawal design
- adaptive trial designs
- single-arm trials with several possible external controls
- ...

Alternative evidence

In a rare disease context, all available evidence should be considered in the JCA. The commonly applied hierarchy ranking evidence according to its sensitivity to bias (see Figure 4) should be considered here but needs to be seen in the disease context.[3] EUnetHTA21 guidance already discusses possible biases in different types of evidence and how to address them.[4]

Some national HTA bodies already realise that such a hierarchy should be adapted to the given disease context. For example, in the Netherlands, the NHCI has developed a framework to systematically weigh up what can be considered "appropriate evidence" in view of the specific intervention concerned.[7]

Box 1 and Box 4 show that HTAs already use alternative methods of interpretation of the available data, to ensure access for rare disease patients.

Box 1. Single-arm trials in SMA[5]

Nusinersen is a treatment for spinal muscular atrophy (SMA), a very rare, progressive neuromuscular disorder. When coming to market, Nusinersen addressed a high unmet need as it was the first disease-modifying treatment to slow down disease progression.[6]

During the HTA with IQWiG in Germany, the developer aimed at proving the added benefits of the treatment for pre-symptomatic patients, among others. However, no RCT evidence or indirect comparison based on RCT data was available for Nusinersen for this subgroup.

The developer included evidence from an ongoing, open-label, single-arm trial for pre-symptomatic patients of a specific type (with two or three SMN2 gene copies). This non-comparative trial alone was not sufficient for assessing added benefit.

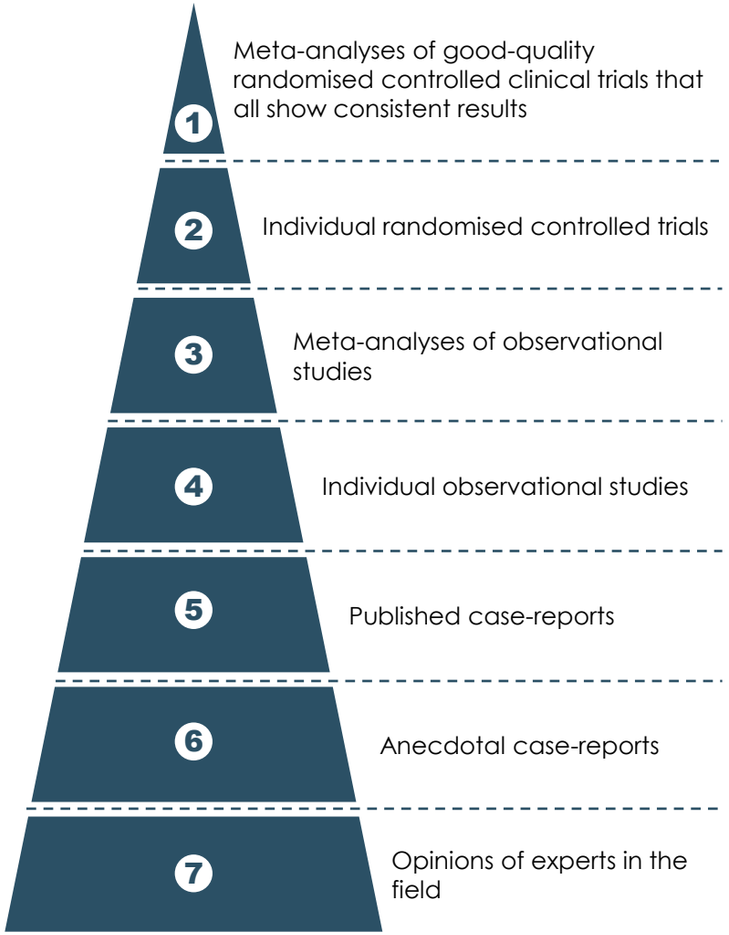
Therefore, IQWiG considered another recent RCT study that had shown significant benefit for early onset SMA patients with two SMN2 copies. A key condition for transferring the result of this study from one patient population to the other was the sufficient comparability of the selected populations. Therefore, the developer constructed an indirect treatment comparison of the two studies focusing only on the patients with two SMN2 copies.

IQWiG granted basic comparability on the assumption that pre-symptomatic patients would develop an early onset of the disease in the natural course of the disease. Moreover, treatment effects in the single-arm study were higher than those of the RCT.

Eventually, IQWiG assigned a non-quantifiable added benefit for pre-symptomatic patients based on this transfer of evidence across subpopulations.

Figure 4. Traditional hierarchy of evidence[8]

Higher-layer evidence is generally less sensitive to bias.



Sources: 1) Abrahamyan (2016): "Alternative designs for clinical trials in rare diseases", Link; EUnetHTA (2022): guidance document D4.6 already includes some alternative trial designs such as cross-over trials, adaptive trails, single-arm trials; 2) EUnetHTA (2022): "D4.6 Validity of clinical studies – Project Plan", Link ; 3) EMA CHMPS: "guideline on clinical trials in small populations", Link; 4) EUnetHTA (2022): guidance document D4.6; 5) IQWiG (2021): "[A20-114] Nusinersen (spinal muscular atrophy) - Benefit assessment according to §35a Social Code Book V", Link; 6) NICE (2019): "Nusinersen for treating spinal muscular atrophy", TA588, Link; 7) NHCI (2015): "Assessment of 'established medical science and medical practice'", Link; 8) EMA CHMPS: "guideline on clinical trials in small populations", Link; and) G-BA(2022): "Verfahrensordnung des Gemeinsamen Bundesauschusses", p.47, Link;

Guidance B: What are the evidentiary expectations in a non-RCT setting?

Valid endpoints

For rare diseases, the choice of the primary endpoint may pose several problems. First, the most appropriate clinical endpoint may not be well-established, validated or even known. Second, the effect of the test treatment may be too uncertain to predict which of several possible outcomes will be affected. Third, even given a validated clinical endpoint and a clear mode of action of the tested treatment, recruitment of a sufficient number of patients may be difficult or the demonstration of this endpoint may take unreasonably long.[1]

The guidance should outline how to prioritise and evaluate **different clinical endpoints**. If preferred clinically relevant or patient-relevant outcomes cannot be directly reached, the guidance must explain when the **use of surrogate endpoints is a valid choice.** The EUnetHTA21 guidance on endpoints determines how the association between a surrogate endpoint and a clinically relevant or patient-centred outcome needs to be assessed and which metric is used. However, it is up to member states to decide whether to accept the validated endpoints.
Today, surrogate endpoints, if validated, are deemed acceptable measures of clinical efficacy or effectiveness by HTA bodies, for instance in France, Germany, and Sweden. For example, although overall survival is preferred as an endpoint, progression-free survival may be accepted in France and the UK if life expectancy may be too short or progression-free survival is validated as a surrogate for overall survival.[2]

The HTA of obeticholic acid for treating primary biliary cholangitis (PBC) at the Scottish Medicines Consortium (SMC) illustrates how surrogate markers may suffice as trial endpoints when direct health outcomes are not feasible to assess in the short term and the treatment addresses an unmet medical need; see Box 2.

Comparators

Active comparators are less frequent among clinical trials in rare disease areas as the standard of care is usually less well-established.[3]

Often, a concurrent comparator group may not be practically or ethically feasible when the trial is planned[4]. A common approach then is to rely on external controls. In the OMP context, such comparisons are likely to be indirect. The reasons are that generally a smaller number of total relevant trials is conducted, and hence available for comparison; among those, higher between-trial heterogeneity in terms of treatment effects can be expected.[5] Alternatively, controls can be based on natural history data of the disease.

Further guidance should be developed that explains the rationale for the choice of certain methods. The methods applied in the JCA should then be accepted by the member states.
Finally, if standards of care are heterogeneous across European countries, the guidance must outline how the European HTA should **specify a list of care standards** against which a given treatment should be assessed

The added benefit assessment of Risdiplam, a disease-modifying treatment for SMA, at IQWiG[6] illustrates several challenges regarding the choice of the ACT for OMP if the standard of care is not uniform or well-established. See Box 3 on the next page.

Box 2. Use of surrogate endpoints[7]

PBC is a rare and life-threatening liver disease that progresses slowly and is estimated at a prevalence of 2-40 in 100,000. The OMP obeticholic acid was targeted at patients who are not sufficiently treated by the existing treatment, ursodeoxycholic acid (UDCA).

The main evidence for obeticholic acid´s HTA at SMC came from a phase 3 RCT (POISE) that included the said patients. Due to the slow disease progression of PBC, the company faced the challenge that relevant direct health outcomes such as liver transplant, decompensation or death could only be assessed in the long term as sufficient events for a meaningful comparison were unlikely within the selected timeframe of the study. Relying solely on these outcomes would significantly increase the time to market of a drug with a high unmet need.

Data from UDCA research suggests that the biochemical markers alkaline phosphatase (ALP) and total bilirubin among patients are associated with disease progression and lower levels of these markers are associated with liver-transplant-free survival and other relevant clinical outcomes.

Hence, instead of selecting direct health outcomes, the primary outcome in POISE was a surrogate marker for disease severity and prognosis: reductions in alkaline phosphatase (ALP) and bilirubin concentration compared to baseline. Trial participants in the obeticholic acid treatment arm had significantly reduced ALP and bilirubin values. This led to obeticholic acid being recommended by SMC for reimbursement in NHS Scotland.

The POISE study was not designed to measure relevant direct health outcomes. This limitation was noted during the regulatory approval stage by EMA and addressed by demanding a phase 3 study on direct clinical outcomes as part of obeticholic acid´s conditional marketing approval.

Sources: 1) EMA CHMPS: "guideline on clinical trials in small populations", Link; 2)) Stafinski et al. (2022): "HTA decision-making for drugs for rare diseases: comparison of processes across countries", Link; 3) Logviss et al. (2018): "Characteristics of clinical trials in rare vs. common diseases: A register-based Latvian study", Link; 4) FDA (2019): "Rare Diseases: Common Issues in Drug Development: Guidance for Industry", Link; 5) Friede et al. (2017): "Meta-analysis of few small studies in orphan diseases", Link; 6) IQWiG (2021): "Risdiplam (spinal muscular atrophy) – Benefit assessment according to §35a Social Code Book V", Link; 7) SMC (2017): "obeticholic acid (Ocaliva) is accepted for use within NHS Scotland", Link;

Guidance B: What are the evidentiary expectations in a non-standard RCT setting?

Box 3. Challenges in comparator choice[1]

During the HTA at IQWiG, Risdiplam, a disease-modifying treatment for SMA, faced three challenges regarding the choice of the appropriate comparator treatment (ACT) as the standard of care was not uniform or well-established:

Challenge 1: Risdiplam has a broad marketing authorisation. However, the standard of care for SMA depends on the subpopulation. Hence, the company had to assign different ACTs for different subpopulations and plan different studies accordingly. IQWiG identified Nusinersen as the ACT for SMA types 1 and 2. For SMA type 3, the ACT would be a treatment of "physician´s choice choosing from Nusinersen or best supportive care (BSC)". BSC consists of individually optimised symptom control and quality-of-life improvement, including physiotherapy or patient ventilation, if necessary. For SMA type 3, the company only used BSC as a comparator, which was not sufficient to derive an added benefit, according to IQWiG.

Challenge 2: Best supportive care for SMA is heterogenous across countries. This may lead to studies not being considered if there is doubt of adequate implementation of BSC in accordance with the national standard.[2]

Challenge 3: Nusinersen, considered the main ACT, is unavailable to a significant share of patients. This restricts inclusion criteria further, decreasing the available sample size. Consequently, NICE specified BSC as the most appropriate comparator in their technology appraisal of Risdiplam.[3]

Risdiplam's benefit assessment needs to be interpreted since no direct trial evidence is available that compares Nusinersen and Risdiplam.

Statistical methods

The obvious shortcomings of standard frequentist statistics in small population scenarios have led to the development of new statistical methods. The applicable alternative methods of interpretation should be accepted by the member states when used in the JCA and the context of the pros and cons for the choice of methods should be well described, considering the limitations in Guidance A so as not to negatively impact the national decision-making.

The NICE technology appraisal of Lanadelumab[4] for preventing recurrent attacks of hereditary angioedema (HAE) shows that alternative statistical methods may be considered when small a sample size constrains the analysis; see Box 4.

RWE to reduce uncertainty over time

The collection of RWD and generation of RWE serve to diminish evidentiary uncertainty over time and are already used across the European HTA landscape. For instance, several countries have put in place conditional market access schemes to allow promising treatments to collect RWE before facing re-assessment of clinical benefits after a specified period.

For example, Nusinersen and Risdiplam are currently both subject to managed access agreements in the UK. An unconditionally positive recommendation had not been possible due to substantial uncertainties about the long-term benefits of the two treatments. The conditional, temporary inclusion of these medicines into the market may generate suitable RWE to address these uncertainties.[3]

Similarly, the evidence submitted on obeticholic acid for treating PBC drew no conclusions on long-term clinical outcomes; see Box 2. Again, RWE may help to address the uncertainty regarding these outcomes.

The guidance must specify how RWE can be used in JCA for initial assessments and updated assessments when more comprehensive RWE can be expected. A harmonised approach to the generation of RWE is needed, starting at the time of JCA, with agreement on the types of data to collect, who collects what, and how the data will be used in updated assessments at the EU level.

Box 4. Use of alternative statistical methods[5]

HAE is a rare genetic disorder that causes swelling in body parts. "HAE attacks" are painful and potentially life-threatening if swelling happens in the airways. Globally, the disease prevalence is estimated at 1 in 10,000-50,000.[5]

Only a subgroup that meets certain disease severity criteria is treated with long-term preventive treatment with an intravenous C1 esterase inhibitor (C1-INH). The treatment Lanadelumab was positioned to target this subgroup, making C1-INH the appropriate comparator.

No direct trial evidence comparing Lanadelumab against C1-INH existed. Therefore, after proving the clinical effectiveness of lanadelumab against a placebo in an RCT (HELP-03), the developer conducted an indirect treatment comparison of HELP-03 against a crossover trial of C1-INH against a placebo. They used a Bayesian indirect comparison to inform the attack rates for both drugs.

The developer faced the challenge that a random effects statistical model would not yield robust estimates due to the sample size being too small in the given setting. Instead, they settled for a fixed effects model, excluding an uncertainty analysis from their favoured specification.

This approach was accepted by the NICE committee, given that both treatment responses to C1-INH and lanadelumab would be computed by this approach.

Treatment effects from the indirect comparison were very similar for lanadelumab compared to those in HELP-03. Also, the indirect comparison yielded lower mean attack rates for lanadelumab than for C1-INH. Hence, lanadelumab was deemed clinically effective compared with C1-INH and recommended for the specified population.

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