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Economic Modelling Considerations for Rare Diseases

The power of **knowledge.**
The value of **understanding.**



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Economic Modeling Considerations for Rare Diseases

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Key Learning Objectives

- 1 Rare diseases and health technology assessment (HTA)
 - How do HTA bodies define rare or ultra-orphan diseases?
 - How do HTA bodies appraise rare diseases products?
- 2 What are the key challenges to developing cost-effectiveness models in rare diseases?
- 3 How do we overcome these challenges?
- 4 Case study example
- 5 Conclusion and recommendations

Rare Diseases and HTA



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The Definitions of Rare Diseases are Not Consistent Across Countries

Country	Definition
 Germany	<p>The Gemeinsame Bundesausschuss (G-BA) has adopted the European Commission (EC) definition for orphan drugs (EC regulation number 141/2000); a maximum of 5 per 10,000 people</p>
 France	<p>The French Ministry of Health reports that a rare disease is a “disease that affects less than 1/2,000 people in the general population”, consistent with the EC definition for orphan drugs</p>
 The Netherlands	<p>The Netherlands has adopted the EC definition for orphan drugs (EC regulation number 141/2000); a maximum of 5 per 10,000 people</p>
 Canada	<p>A rare disease has a defined prevalence of less than 2,000 individuals</p>
 Australia	<p>A rare disease has a defined prevalence of less than 2,000 individuals</p>
 England and Wales	<p>The National Institute for Health and Care Excellence (NICE) Highly Specialised Technologies (HST) criteria state the target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the National Health Service (NHS)</p>
 Scotland	<p>Orphan medicine: a medicine affecting fewer than 2,500 people in a population of 5 million Ultra-orphan medicine: a medicine used to treat a condition with a prevalence of 1 in 50,000 or less (or around 100 people in Scotland)</p>

G-BA, 2019; CADTH, 2018; Ministère des Solidarités et de la Santé, 2018; NICE, 2017a; SMC, 2016; Therapeutic Goods Administration, 2016; ZonMw, 2013.

HTA in Rare Diseases

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Most orphan products are not found to be cost-effective when measured by standard thresholds

 - High drug costs from sales to a limited number of patients
- 

Markets such as the US and EU have introduced incentives and favourable tax initiatives to encourage the development of orphan products
- 

Orphan products must still undergo formal HTA economic evaluation in parallel to or after regulatory approval in some, but not all, EU countries
- 

There may be challenges in developing evaluations of sufficient methodological quality and certainty to meet HTA requirements

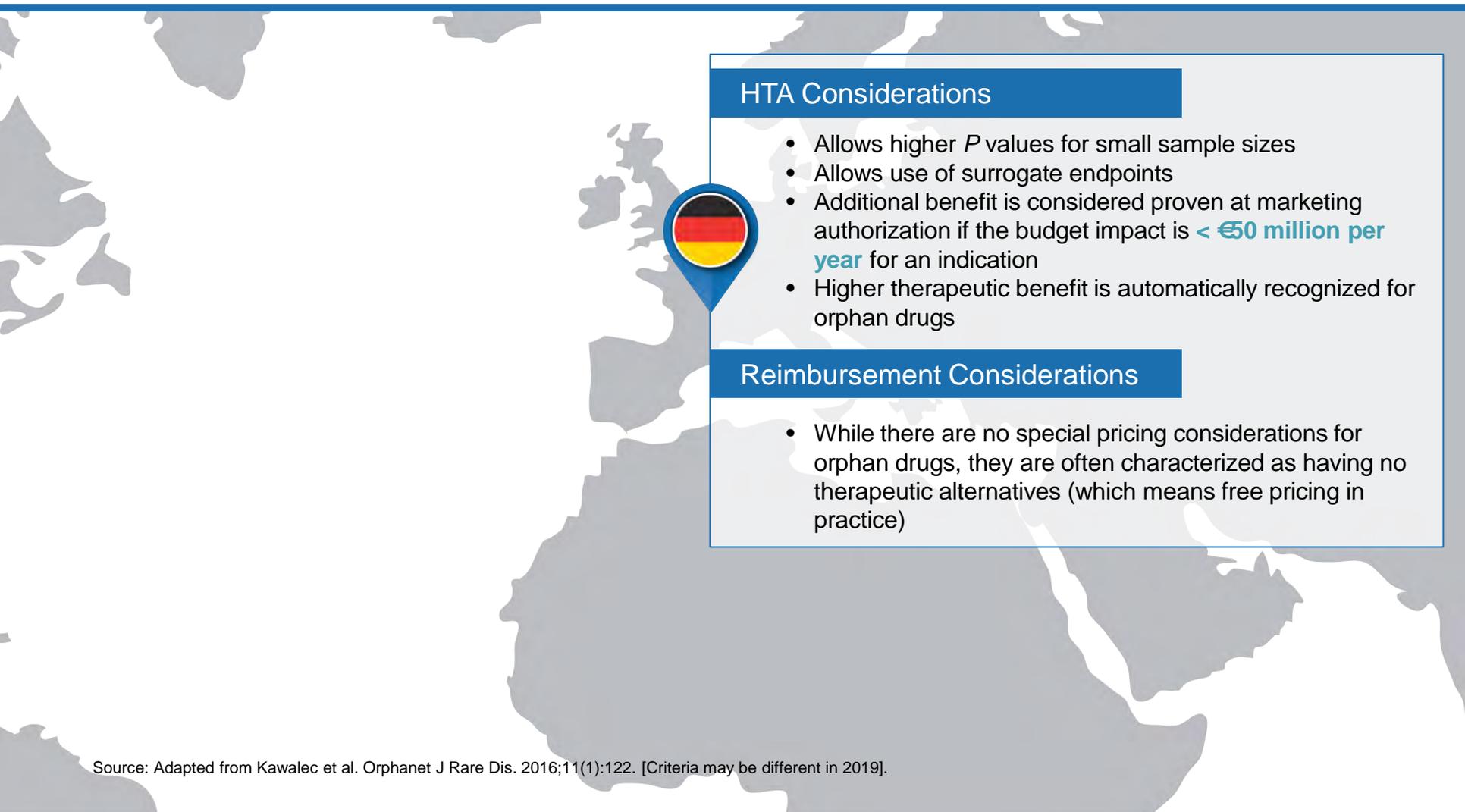
Country-Specific HTA Requirements in Europe Summary

Assessment Criteria/Tools	Country						
	Germany	UK	France	Italy	Spain	Netherlands	Nordic Countries ^a
Assessment of therapeutic benefit	✓	✓	✓	✓	✓	✓	✓
Assessment of patient benefit	✓	✓	✓	✓	✓	✓	✓
Perspective	P	P	P	S/P	S/P	S	S
Cost-effectiveness model	—	CUA	CUA	CEA, CUA	CEA, CUA	CEA, CUA	CEA, CUA
Budget-impact model	Cost calculation	✓	✓	✓	✓	✓	Cost calculation
Therapeutic alternatives	✓	✓	✓	—	—	✓	✓
Systematic literature reviews	✓	✓	✓	✓	✓	✓	✓
Quality-of-life evaluation	—	EQ-5D	EQ-5D	EQ-5D	EQ-5D/ SF-36	EQ-5D	EQ-5D
Dossier required	✓	✓	✓	✓	✓	✓	✓
Reference pricing required in dossier	Supportive information	No	Main criterion	Supportive information	Supportive information	Main criterion	Sweden: no Denmark, Finland, Norway: yes
Time from submission to reimbursement	0 (12-month free pricing)	180-250 days	180-250 days	180-250 days	180-400 days	90-400 days	180 days

^a The Nordic countries include Denmark, Finland, Norway, and Sweden.

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; P = payer; S = societal; SG = standard gamble; TTO = time trade-off; UK = United Kingdom.

Special HTA and Reimbursement Considerations for Orphan Drugs



HTA Considerations

- Allows higher P values for small sample sizes
- Allows use of surrogate endpoints
- Additional benefit is considered proven at marketing authorization if the budget impact is < €50 million per year for an indication
- Higher therapeutic benefit is automatically recognized for orphan drugs

Reimbursement Considerations

- While there are no special pricing considerations for orphan drugs, they are often characterized as having no therapeutic alternatives (which means free pricing in practice)

Source: Adapted from Kawalec et al. Orphanet J Rare Dis. 2016;11(1):122. [Criteria may be different in 2019].

Special HTA and Reimbursement Considerations for Orphan Drugs

HTA Considerations

- Additional benefit is considered proven at marketing authorization if the budget impact is **< €30 million per year** for an indication
- Accelerated HTA process is available for all innovative drugs



Reimbursement Considerations

- Ministry of Health decides on the reimbursement, taking the SMR and ASMR into consideration
- Authorization can be issued for temporary use for life-threatening conditions and/or where there is no therapeutic alternative

ASMR = improvement in medical benefit; SMR = actual medical benefit.
Source: Adapted from Kawalec et al. Orphanet J Rare Dis. 2016;11(1):122. [Criteria may be different in 2019].

Special HTA and Reimbursement Considerations for Orphan Drugs

HTA Considerations



- Lower levels of evidence are accepted for clinical trials and in economic evaluation
- NICE budget-impact test: if the budget is **> £20 million** in any of the first 3 years, NHS England may engage in commercial discussions with the manufacturer

Reimbursement Considerations

- If accepted into the HST program, ICER threshold increased to **£100,000 per QALY gained**
- Treatments deemed to provide significant QALY benefits assessed against a maximum threshold of **£300,000 per QALY gained**
- A single HST evaluation can only cover a single technology for a single indication
- Only 3 HST appraisals per year are referred

HST = highly specialized technology; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Adapted from Kawalec et al. Orphanet J Rare Dis. 2016;11(1):122. [Criteria may be different in 2019]; NICE, 2017b; SMC 2016; 2019.

Special HTA and Reimbursement Considerations for Orphan Drugs



HTA Considerations

- Lower levels of evidence are accepted for clinical trials and in economic evaluation
- Patient and clinician and engagement
- Revised assessment process for ultra-orphan products

Reimbursement Considerations

- None

Source: Adapted from Kawalec et al. Orphanet J Rare Dis. 2016;11(1):122. [Criteria may be different in 2019]; NICE, 2017b; SMC 2016; 2019.

Economic Modelling in Rare Diseases



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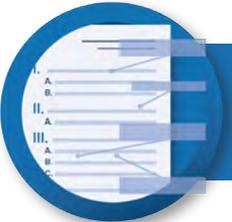
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Do We Need to Develop Economic Models for Rare Diseases?



HTA bodies require an economic component of the submission

- More emphasis on unmet need
- Manufacturers should make best use of the available data to minimise uncertainty



Companies need to show that the clinical outcomes measured in the trials

- Are appropriate for the disease area
 - Clinically meaningful
 - Important to sufferers (patients and their caregivers)
- Can be translated into health benefits for the patients
- Are adequately extrapolated beyond trial duration
 - Long-term benefits

QOL = quality of life.

Hurdles to Modelling in Rare Diseases

Paucity of Data



Clinical data

- Understanding the natural history of the disease
- Controlled/direct head-to-head trials may not exist
- Duration of trials often short <1 year
- Lack of “hard” clinical endpoints



QOL data

- Extra burden on patients/caregivers



Healthcare resource use





Clinical Trial Data

Clinical Data – Beyond Trial End

Challenges

Single-armed

- How do we compare to current standard of care or other treatments?

Short-term

- How do we extrapolate trial results over the longer term (lifetime)?

Solutions

Progression of the disease

- Companies have supported natural history registries/datasets
 - Providing long-term data – proxy for standard care

Observational studies / single-arm trials

- If at least one patient-level dataset is available

Matching adjusted indirect comparison (MAIC) - Signorovitch et al., 2010; 2011; 2012; Malangone and Sherman, 2011.

Simulated treatment comparisons (STC) - Ishak et al. 2015.

NICE DSU TSD18, 2016 – overview of MAIC and STC - http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD16_Treatment_Switching.pdf.

Population-Adjusted Indirect Comparison Example

Patient Characteristics	Natural History Published Summary Data	Unadjusted Own Patient-Level Data Summary	Adjusted Own Patient-Level Data Summary
Age (years)	45.6 (30–55)	58.5 (50–65)	45.6 (30–55)
Gender - Male	80%	40%	80%
Years with condition	3.2	4.3	3.2
Outcomes			
1-year survival rate	56%	55%	64%
2-year survival rate	23%	22%	30%



Quality of Life Data

Patient Quality of Life – Utility Estimates

Challenges

- No preference-based utility measure within trial (e.g., EQ-5D, SF-6D)
- No mapping of disease specific questionnaire to generic utility measure
- Many rare conditions affect children, cause cognitive impairment or severe illness
- Some states or patients may not be measurable in a trial

Solutions

- Ideally – plan early – consider including a preference-based measure in the trial
- Literature search for existing utility values (should be a standard undertaking)
- Observational utility study – e.g. via patient advocacy group
- Vignette study – valuation of health state descriptions, usually by general public

ISPOR Guidelines: Wolowacz et al., Value Health, 2016; 19:704-19.

Vignettes Play A Bigger Role in Rare Diseases

Overview of Methodology

- Develop health state descriptions
 - Quality is critical
 - Review qualitative QOL literature and content of condition-specific QOL instruments
 - In-depth qualitative interviews with patients, clinicians, nurses, advocates
 - Quantitative data - condition-specific QOL data for patients in health state
- Validate health state descriptions
- Conduct preference-based valuation
 - E.g. TTO, SG
 - Usually in general population

Example Health State

- 
- You have problems walking and tire quickly
 - You occasionally require a wheelchair for mobility
 - You require help to wash, dress, and care for yourself normally
 - You experience intermittent pain
 - You spend a lot of time worrying about your health getting worse, and you sometimes feel low or depressed

Brazier & Rowen, 2011. NICE Technical Support Document 11. nicedsu.org.uk
TTO = time trade-of; SG = standard gamble

Vignettes - Advantages and Disadvantages

- Advantages

- Comparatively quick and easy
- Can be prepared with little or no patient level data
- Can estimate utility values that may otherwise be difficult to measure
- Can be designed to incorporate concerns of importance to patients

- Disadvantages

- Cannot represent full range of experience among individual patients
- Differences among valuation methods → inconsistency in decision-making
- Needed for each market
- Do not meet some HTA agency standards (e.g. NICE)

Caregiver Utility

- Many HTA bodies consider caregiver QOL, where relevant
 - (CADTH, NICE, PBAC, Zorginstituut Nederland [ZiN]) – “spill over” impacts affecting caregivers
- Caregiver QOL is often relevant in rare diseases
 - NICE HST precedence have allowed 2 caregivers to be considered
- How to incorporate caregiver utility into a model?
 - Consideration needs to be given as to whether caregiving is a disutility to their general QOL
 - If a new intervention extends life but at a poor quality that requires a high level of caregiving – could have a negative impact on the QALY value
 - NoMA guidelines (2018) state - effects on the caregiver’s quality of life of increased life expectancy in itself should not be taken into account

Resource Use Data

Challenges

- Lack of healthcare resource utilization (HCRU) data in trial
- Lack of published studies

Solutions

- Literature review – burden of disease data
- Registry data
- Commission separate study
 - Medical record abstraction/ chart review survey
- Seek clinical opinion
- Analogs

Overcoming the Hurdles – Data Elicitation



Patient advocates

- Help understand what is important to the patient
- Keen to be involved
- Help understand indirect/societal costs

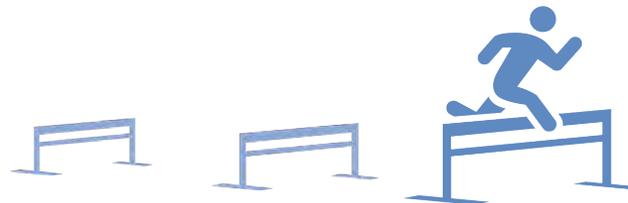


Clinical opinion

- Help define disease progression – health states
- Advisory boards
 - Model structure validation
- Elicitation methods
 - Delphi panels / mathematical approaches



Analogs – leverage data from other disease areas



Collaboration Between Industry, Academics, Patients, HTA Organisations – The Future?

- Project HERCULES
 - HERCULES = HEalth Research Collaboration United in Leading Evidence Synthesis
 - A collaboration between Duchenne UK, academia, clinicians, and interested pharmaceutical companies to increase the chances of patients with DMD accessing innovative treatments
- Aims to deliver
 - A bespoke, validated, QOL metric
 - A natural history model developed for bringing together the largest collection of clinical data in DMD for multiple registries and trials
 - A burden-of-illness study that will better capture the true impact of DMD on patients and their families
 - A disease-level economic model

DMD = Duchene's Muscular Dystrophy.
<https://www.duchenneuk.org/project-hercules> .

Key Questions / Learnings From HTA Bodies

Common questions HTA bodies are asking themselves

- Sensitivity analysis
 - Is it adequate?

- Estimate of population undergoing treatment
 - Although rare, the population may be heterogeneous
 - Will all patients be treated with the new intervention?
 - Will “late stage” patients benefit, will they receive treatment?
 - Are there any clinical benefits for these patients to be gained?

- What are the treatment stopping rules?
 - How will they be implemented in routine practice?



Case Study

NICE Managed Access Agreement for elosulfase alfa for Treating Mucopolysaccharidosis Type IVa (MPS IVa)

- MPS IVa is an inherited lysosomal storage disease that causes progressive tissue damage, leading to dependence on a wheelchair
- A 24-week placebo-controlled trial took place:
 - The placebo was not representative of standard of care due to the high level of care patients received
 - Data from a natural history study was used for the standard of care treatment arm
- Health state utility values were based on results from a subset of patients from burden-of-illness studies
- Caregiver disutility values were derived from a multiple sclerosis study (analog)
- A Delphi panel process was applied to:
 - Derive parameter values in the economic model, where data was absent
 - Validate certain modelling assumptions
- A registry was started to collect clinical, cost, and QOL data

- A cost consequence model was developed to support the NICE HST submission:
 - Base case: Established clinical management associated with £618,812 in costs and 9.75 QALYs (elosulfase alfa drug acquisition cost: £14,014,636; total elosulfase alfa costs: commercial in confidence)
 - The Evidence Review Group (ERG) considered assumptions to model clinical effectiveness were uncertain and not fully consistent with the evidence
 - In response to the second evaluation consultation document, and facilitated by NICE, a managed access agreement was developed by stakeholders, including the manufacturer, NHS England, the MPS Society, and a group of clinical experts

NICE, 2015.

NICE Managed Access Agreement for elosulfase alfa for Treating MPS IVa

- NICE has approved reimbursement of elosulfase alfa subject to the collection of auditable measures to assess the compliance of a managed access agreement that will remain in force until earlier of:
 - Publication of the NICE HST for elosulfase alfa
 - A maximum of 5 years
- The managed access agreement includes:
 - A protocol that sets out the clinical criteria for starting and stopping treatment with elosulfase alfa
 - Assurance from the “Marketing Authorisation Holder” that it will collaborate with the MPS Society and NHS England to collect anonymized data and continue to support the MPS IVA registry (MARS study). The data will be used by NICE to inform a review no more than 5 years after publication of the guidance
 - Agreement between the licensed owner of and NHS England to set the total costs of elosulfase alfa during data collection, which is in addition to the discount in the patient access scheme, to manage financial risk

NICE, 2015.

Best Practice Recommendations

Plan Early!

- Where are the data gaps?
- Access to registry data
- Access to patient advocacy groups
- Identify key opinion leaders
 - Both clinical and health economic
- Initiate QOL studies
- Initiate resource use studies

Conclusions

- ✓ Budget-impact analysis is important
- ✓ Transparency of assumptions
- ✓ Review HTA critiques of other rare diseases
- ✓ Continued collection of clinical, HRQOL and Resource Use data



Q&A

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