



# Clinical and economic issues complicating cost-effectiveness evaluation of orphan diseases

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## Abstract

Cost-effectiveness evaluation of orphan medicinal products is confronted with a large confidence interval on the incremental cost-effectiveness ratios (ICERs), or extremely high ICERs and therefore rejection of products for uptake in the health insurance package (coverage) by health authorities in Europe. Examples from the United Kingdom (UK) and The Netherlands illustrated that straightforward application of the decision criteria might not always be possible, resulting in a large variety of coverage decisions that were neither transparent nor consistent with the criteria. This observation required more insight into what drives the high ICERs and what policies may support the appropriate use of orphan medicinal products. The most relevant clinical and economic issues that are perceived to complicate the cost-effectiveness evaluation of orphan medicinal products are discussed. Theoretically, two possible solutions are available: 1) circumvent or 2) keep the standard assessment criterion costeffectiveness.

In analogy to the Europe Medicine Agency (EMA) registration approach of orphan medicinal products that are hampered by limitations in the clinical data at the time of registration, we suggest to stick to the use of standard uniform criteria, but that efforts should be directed at optimising the input to the cost-effectiveness evaluation. Subsequently potential policy approaches are developed.

## Introduction

Cost-effectiveness evaluation of orphan medicinal products is confronted with uncertainty (large confidence interval of the incremental cost-effectiveness ratio, ICER), or extremely high ICERs. When cost-effectiveness is a criterion for uptake of new orphan medicinal products in the health insurance package (coverage), orphan medicinal products risk being rejected by health authorities in Europe.

A prominent example is the Dutch assessment of the cost-effectiveness of the orphan medicinal products for the orphan diseases 'Fabry and Pompe'. In 2012 the National Health Care Institute (Dutch Zorginstituut Nederland, ZINL) concluded that the ICERs of these treatments extend far beyond the Dutch bandwidth (1) of €10,000 per QALY gained in case of a low disease burden (0.1) to €80,000 per QALY gained in case of a high disease burden. ZINL advised the Minister of Health to exclude these products from coverage due their lack of cost-effectiveness (2,3). Under heavy societal pressure, the ZINL adjusted their advice into preliminary continuation of the already existing conditional coverage since the time of launch in 2001, while installing at the same time a special fund for these orphan medicinal products, limitations in use and price negotiations with the manufacturers. The Minister of Health disagreed with the first two suggestions, referring to the general legal basis of coverage of medicinal products that also applies to orphan medicinal products (4). Financial agreement between the Minister of Health and manufacturer was achieved shortly afterwards (5).

Another example illustrates the need for consistency with regard to the performance of cost-effectiveness evaluation. In the United Kingdom (UK), the National Institute for

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Health and Care Excellence (NICE) has calculated an ICER of £203,009 per QALY gained (€241,580) for the Fabry disease orphan medicinal product, while the Dutch health authorities calculated an ICER of €3,3 million per QALY gained (3,6). This huge difference raises questions about the methods used and leaves stakeholders with questions about the formal role and weighting of standard assessment criteria. Such large differences cannot be explained by differences in discounting, treatment patterns, and unit costs, but might be explained by differences in the eligible patient groups assessed (indication) and the valuation of the health benefits. This observation requires more insight into the cost effectiveness drivers and what policies may support the appropriate use of orphan medicinal products. Our multidisciplinary working group discussed the most relevant clinical and economic issues that are perceived to complicate the cost-effectiveness evaluation of orphan diseases and orphan medicinal products and to drive the high ICERs (7). Subsequently potential policy approaches are presented.

### Basic concept of cost-effectiveness

Cost-effectiveness of a medicinal product is based on the costs that will result from its use, and the potential savings that will be made compared with other products and/or treatments and the health benefits to the patient. The most used measure of this health benefit is the “quality-adjusted life year,” or QALY. The lower the ratio of a cost per QALY, the more cost-effective a health intervention is said to be. Threshold values are informally used in coverage decisions. Medicinal products with ratios above these threshold values are not given coverage. These threshold values vary considerably from country to country. Values ranging from \$50,000 to \$100,000 per QALY gained (€37,000 to €74,000) are sometimes used as a threshold in the United States (US)(8), whereas in the UK NICE has adopted a cost effectiveness threshold range of £20,000 to £30,000 per QALY gained (€23,800 to €35,700) and in case of end-of-life treatment an ICER up to £55,000 (€65,450) (9). Other proposals include a differential threshold value between diverse disease states, treatment characteristics and disease burden, for example the Dutch bandwidth of €10,000 to €80,000 per QALY (1) gained.

### Orphan diseases

Orphan disease is defined in the EU Orphan Regulation 141/2000 (10) as:

- A disease that is life-threatening or chronically debilitating; s
- Prevalence of the condition in the EU of less than 5 in 10,000 or unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and
- No satisfactory method of diagnosis, prevention or treatment of the condition concerned has been authorized in the EU, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Additionally, other factors like heterogeneity of patient population, multiple affected organ systems, heterogeneity of disease state and presented symptoms and broader health and financial impacts on the family and carers of the patient complicate the assessment of many orphan diseases. However, it is important to consider that each separate issue in itself or the combination of issues might not be unique for orphan diseases but apply also to non-orphan diseases.

### Orphan diseases and cost-effectiveness

The above mentioned examples from the UK and The Netherlands reflect the difficulties in demonstrating cost-effectiveness of treatments for orphan diseases, and the subsequent rejection of orphan medicinal products for coverage due to (extremely) high ICERs. Furthermore, when orphan products are covered, they illustrate the lack of transparency, in some countries, in the relationship between cost-effectiveness and health authorities' decisions for covering medicinal products. This is more likely to occur when there is no clear, formalised framework, which justifies the application of the common thresholds for standard cost-effectiveness outcomes to all medicinal products.

Stakeholders, such as manufacturers and patient organisations, have disputed the appropriateness of the cost-effectiveness criterion in national coverage assessment procedures for orphan medicinal products. They have suggested that treatment of orphan diseases may require a different approach in coverage decisions and health technology assessment (HTA) procedures. Before elaborating on a possible approach, we suggest that the first step in search of solutions is a more in-depth investigation of the cost-effectiveness issues and the 'drivers' of high ICERs for orphan medicinal products rather than creating new frameworks (7).

### Relevant issues for orphan medicinal products and diseases

It is important to consider that each separate issue in itself or the combination of issues might not be unique for orphan diseases. We are aware of non-orphan diseases, for example some cancers or multiple sclerosis, that may also be affected by the same combination of issues. However, the key problem of small numbers of patients for study and for generating fair future revenues makes the difficulties more pronounced in orphan diseases.<sup>27</sup>

#### Clinical issues

##### Sample size and heterogeneity (7)

The sample size of clinical trials and observational studies is limited in orphan disease, because of

- A limited number of potential patients with a specific disease;
- The spectrum of disease may vary considerably in the severity of the disease, duration of the disease, as well as in other prognostic factors such as age, disease progression and

type of symptoms, as most orphan diseases have an impact on various organ systems;

- Patients to be included are in various stages of the disease at the time treatment can be initiated;
- There is a lack of historical epidemiological data which would allow an estimation of the expected course of the disease (with or without treatment), and
- There is a lack of biomarkers to monitor disease progression.

For example in Pompe disease, patients may differ substantially in the severity of the disease and the type of symptoms: A two-year old child, who has just learned to walk, staggers and appears to walk with a limp compared to a 37-year-old man who falls asleep during the day and has trouble breathing when he lies down.<sup>11</sup>

As a consequence, it is often not possible to recruit a sufficiently large, homogeneous group of patients - such as only pre-symptomatic patients, or only patients with moderately severe symptoms - to test clinical efficacy hypotheses using conventional statistical methods.

#### Stratification (7)

In order to identify the at risk persons for developing the disease or defining the persons that benefit most from the therapy, more research is required in diagnostic testing, biomarkers and clinical efficacy and quality of life 'markers', corresponding with the principles of stratified medicine.

#### Study design (7)

Although the RCT (randomized controlled trial) is generally accepted to produce the least biased clinical efficacy data, an RCT in orphan diseases cannot always be performed due to, especially sample size constraints or ethical reasons against a 'best supportive care', once an active therapy has become available. Uncontrolled clinical studies, open label studies and also registries, serving as best available evidence may be alternative options. In these non-RCTs the sample size issue may be partially solved, because some heterogeneity can be controlled for in statistical analysis, but handling of specific methodological issues (e.g. potential bias and confounding variables), as well as guarantee of scientific integrity (e.g. the exclusion of conflict of interest from sponsors) is required. Unfortunately data from registers or observational studies are ranked with a lower level of evidence.

#### Outcome measures (7)

##### *Choice of endpoints*

The choice of the primary endpoint may pose considerable challenges in the design of clinical studies in orphan diseases. In some cases extra time is needed to accumulate sufficient patient numbers to identify the 'most appropriate' clinical endpoint. Equally, as most orphan diseases have an impact on various organ systems, there may be multiple valid endpoints and thus difficulty in choosing a single primary endpoint, contributing to the statistical power problem.

#### *Effect size and responder definition*

Aside from issues of selecting the appropriate primary endpoint, heterogeneity in the study population may have a significant bearing on the size of the treatment effect estimated. When orphan medicinal products are granted marketing-authorisation based on phase 2 rather than on phase 3 studies, a clear understanding of which type of patient benefits the most is still lacking.

Therefore, there is a great need for more research in the area of biomarkers and/or clinical efficacy markers in order to select the appropriate responders.

#### Patient benefits (7)

As outlined above, there will be great difficulty in defining and measuring clinical outcome and observing a change which is significant by conventional standards.

This is the reason economists prefer the use of a generic preference-based, multidimensional measure of health status, which can then be reflected in health benefits. From this perspective, the EQ-5D (EuroQol five dimensions questionnaire) and the SF-6D (Short Form six domains) outcomes are important in the decision-making process, but disease-specific Quality of Life (QoL) outcomes can be relevant as well. Health-Related Quality of life (HRQoL) is a patient-reported outcome measure that gives the voice to the patient on the impact of disease and treatment on their daily life (12). The measurement of statistically significant clinical outcomes and the above-mentioned issues related to small sample size and heterogeneity of the patient population are even more a challenge for the measurement of HRQoL using disease specific instruments. However, in cost-effectiveness modelling uncertainty can be dealt with by probabilistic sensitivity analyses. The recent European network for Health Technology Assessment (EUnetHTA) guideline (Feb 2013)(13) recommends the relative effectiveness assessment of medicinal products by using both disease-specific health-related quality of life and utility measures (EQ-5D and SF-6D). This recommendation applies either when the purpose is to inform patients and health care professionals about the HRQoL benefit of an intervention or when the purpose is to inform health care policy makers about the patient perspective on disease activity and treatment effectiveness. However, only generic measures are likely to capture the multiple dimensions of QoL impact in heterogeneous patient groups. The QoL of the parents and siblings may also be heavily affected in children with orphan disease, which suggests that ideally this should be included in the analysis as well, although this is not specific for orphan disease.

#### Relevant gain (7)

In addition to the relative effectiveness assessment of medicinal products by using health-related quality of life and utility measures, determination of the minimum relevant gain for these measures provides the basis for further optimising the use of orphan medicinal products in those patients that

benefit to an extent that is defined as relevant. A relevant gain will be registered by the use of appropriate outcome measures e.g. a change in EQ-5D score. Professionals can use the pre-specified relevance level of gain for decision-making on starting, continuation or stopping therapy and for designing the treatment protocol and treatment guidelines. This can aid resistance to pressure from patient relatives on the one hand and payers (hospital board, health insurer) on the other hand on whether treatment should be terminated.

*Example (2,11)*

What is a relevant improvement in the parameter “6 minute walking test” in Pompe disease? An improvement in the patient’s ability to walk an additional 20 meters could potentially mean the difference between being able to walk to the car and go to work rather than being compelled to stay at home.

The question is who decides what a relevant change is: the patient, the family, the treating doctor, clinical experts, regulatory authorities, HTA bodies, the public, or all of them? For the definition of a relevant gain we need to know the social significance of clinical changes observed by the social decision-makers (e.g. patients and their carers).

Determination of relevant gain is useful in improving the cost-effectiveness ratio in a well-defined and transparent manner, for reducing budget impact and for improving affordability of expensive orphan medicinal products by health authorities. Table 1 illustrates how relevant gain can be integrated as criterion in decision-making.

**Table 1.** Diagram using statistical significant difference and relevant gain as criteria for assessment of outcomes

Effectiveness outcomes	Outcome ≥ relevant gain	Outcome < relevant gain
Statistical outcomes		
Statistical significant difference	+ +	+ -
No statistical significant difference	- +	- -

**Economic issues**

Costs (7)

A major issue for cost-effectiveness evaluation is getting good quality costing data (resource use data). Each country has its own rules for costing depending on the decision-making perspective. Ideally the cost assessment is based on the so-called opportunity costs of utilising a technology, which are defined as the benefits to be gained from the best alternative use of the resources and has preferably the societal perspective. Orphan products should be evaluated using the same perspective as that used to evaluate other technologies in a particular country. A study from a third party payer’s perspective, which only

includes direct medical costs, would underestimate the true value of a new treatment in orphan disease. For example, when applying the societal perspective to a treatment for children, it is important to consider short-term indirect costs (e.g. time spent by the child undertaking treatment, with loss of educational and leisure activities; productivity losses for parents caring for the child) and long-term indirect costs (e.g. productivity loss as a result of restricted employment opportunities because of reduced educational attainment or physical disabilities).

In orphan diseases, primary cost data collection may be necessary due to the lack of historical databases containing information on the health care utilisation costs of current standard care. The prospective collection of cost data might well be achievable, but in some cases no effort is put into collecting direct medical and non-medical costs as well as indirect costs, if the medicinal product costs are so high that other costs would only contribute a negligible part of the total costs. It is a strong assumption to ignore the non-product costs a priori. It is only possible to draw this conclusion after a sensitivity analysis, so full costing is advisable. The methodological issues for the cost assessment in orphan disease are not much different from other diseases.

**Dilemma**

‘If clinical and economic issues complicate the application of standard cost-effectiveness evaluation of (orphan) medicinal products, principally because of the limitations to the clinical data available when products are launched, and the associated uncertainty resulting in a large confidence interval on the ICER and extremely high ICERs induce authorities to make a negative coverage decision, what solutions are available? Theoretically, two possible solutions are available: 1) circumvent the standard assessment criterion - cost-effectiveness- by adding other criteria reflecting social values, on which most current proposals for Multi Criteria Decision Analysis (MCDA) are based, or 2) keep the standard assessment criterion - cost-effectiveness- and put effort into optimisation of the inputs for the cost-effectiveness evaluation’(7).

**Discussion**

‘In response to these cost-effectiveness issues, stakeholders have disputed the appropriateness of the emphasis that is put on the cost-effectiveness criterion in national coverage assessment procedures. Currently, several European countries have initiated the development of alternative, value frameworks, containing attributes and agreed weights using a MCDA approach (14, 15), or policy tools for circumventing cost-effectiveness in coverage procedures for orphan medicinal products. These additional attributes include rarity, disease severity, and the availability of other alternative treatments, level of unmet medical need, and the level of impact on the condition that the new treatment offers. Unfortunately, these attributes, (as well as their weights), have not been selected through a rigorous assessment of social preferences. Thus,

although the attributes might well be considered important, and a systematic and transparent system of weighted social preferences might help frame a more structured dialogue between stakeholders and health authorities and payers, much work is needed before such a system can be evolved, which can simultaneously deal with the major issues of data quality (lack of strong or convincing clinical evidence), opportunity cost (high price of the product, resulting in high incremental cost-effectiveness ratio) and equity of access. It has taken many years to develop a measure of health benefit (the QALY) which is fit for purpose in many different decision contexts – and it still has many acknowledged imperfections. To move to an MCDA approach, a measure of a similar reliability must be developed for each of the new dimensions of value introduced into the analysis. It can be questioned whether new framework and decision models do offer immediate solutions to the above mentioned problems.

We suggest instead that cost-effectiveness should remain part of the standard assessment criteria set for coverage decisions, consisting of effectiveness, cost-effectiveness and budget impact, that is used for so-called ‘mainstream medicinal products’, i.e. medicinal products that are not hampered by limitations in the clinical data at the time of launch and that efforts should be directed at optimising the input to the cost-effectiveness evaluation. This approach corresponds to EMAs’ approach with respect to the marketing authorization procedure. All applications for marketing-authorisation, whether the products have an orphan designation or not, go through the same EMA committee and through the same assessment procedure – the Committee for Medicinal Products for Human Use (CHMP). The EMA states in the Orphan Regulation that no special assessment for marketing authorisation of orphan medicinal products exists and that such products should be subject to the same assessment as other medicinal products to guarantee that there will be no ‘second rate’ assessment. In applying the standardised assessment methodology and procedure for marketing-authorisation, the EMA has shown it is able to deal with product assessment situations in which the standard requirements cannot be met due to limitations of the clinical data at the time of launch. In their ‘Guideline on Clinical Trials in small populations’, it is concluded that there are no special methods for designing, carrying out or analysing clinical trials in small populations. Approaches are indicated for increasing the efficiency of clinical trials. It is recommended that the need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results; the latter being the most important. In situations where obtaining controlled evidence on the efficacy and safety of a new treatment is not possible, the regulatory assessment is allowed to accept different approaches as long as it is ensured that the patients’ interests are protected. In such situations, treatment conditions and data collection should be standardised and data should be of high quality and adhere to GCP standards.

Whatever the type of orphan medicinal product, it is expected that the outcomes of the conventional analysis will be

driven by the robustness of the clinical evidence and the actual price of the product. Although the outcomes of these standard criteria might not show sufficient evidence for effectiveness and might not meet the national threshold for cost-effectiveness, at least outcomes are available that provide a reference versus standard therapy or best supportive care. On the condition that abuse is avoided (high pricing, not fulfilling a medical need), we suggest that health authorities accept the initial levels of clinical evidence and cost-effectiveness outcomes as interim outcomes that need further confirmation in a conditional coverage period. This approach is also found in the registration procedure of the EMA in case of limitations of the clinical data at the time of launch.

Similarly, prior to this temporary coverage period, a treatment protocol including defined relevant gains as indicator to stop treatment and as a facilitating instrument to identify subgroups of patients needs to be established before further clinical, quality of life and economic data may be gathered in a health outcomes research protocol. At a later stage, for example after 4 years, all newly gathered data may be used as inputs for optimising the input for the standard assessment criteria set and subsequently for a final coverage decision by the health authorities.

We suggest that health authorities apply an ‘EMA-like’ approach to the evaluation of the standard criteria in the coverage assessment of orphan medicinal products and to grant an ‘EMA-like’ model for conditional coverage to (orphan) medicinal products in case of limitations of the clinical data at the time of launch<sup>(7)</sup>.

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#### Author's contributions

Mark Nuijten and Marja Pronk wrote the manuscript and co-developed the concept. John Hutton, Peter van Hasselt, Cor Oosterwijk, and Frans F.H. Rutten developed the concept and contributed to the content of the manuscript and reviewed the manuscript.

#### Competing interests

The authors declare that they have no competing interests.

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