Research Paper 13/03

Multi-Criteria Decision Analysis to Value Orphan Medicines

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May 2013

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Abstract

Objectives

The purpose of this research is to identify the attributes to include in an orphan medicinal product (OMP) value framework, determine their relative importance via a multi-criteria decision analysis (MCDA) process, and test whether an MCDA approach can practically support decision making.

Methods

The project included literature searches on the natural history and burden of 40 rare diseases and how payers assess treatment value as well as three workshops. Workshops also were held: the first with GlaxoSmithKline managers working on OMPs, the second with EU clinical and health economics experts, and the third with representatives of rare diseases patient groups in the European Union. Participants refined the attributes, weighted them, scored two case study OMPs in terms of those attributes, and tested the sensitivity of the overall ratings to changes in weights and scores.

Results

Eight non-monetary attributes were agreed: four concern the disease being treated and four the treatment itself. Workshop participants agreed consensus weights for the attributes. The patient group representatives and the clinical and health economics experts both attributed about half of the weight to attributes reflecting the disease being treated, and half to attributes of the treatment. Patient group representatives gave greater weight than the experts to patients' quality of daily life and less weight to clinical factors. The weighted attributes were readily applied by workshop participants to two example OMPs and yielded distinct ratings of their respective values.

Conclusions

An OMP value framework with agreed attributes and weights is a viable proposition using an MCDA approach, and could improve clarity and transparency in decision making about the value of OMPs.

Introduction

This paper presents an experimental study that tests a multi-criteria decision analysis (MCDA) approach (Devlin and Sussex, 2011) to establish an explicit framework for informing value definition of orphan medicinal products (OMPs) and providing an explicit understanding of trade-offs for decisions on their eligibility for funding.

All health care systems' health technology assessment (HTA) and reimbursement decisions depend on an implicit, if not explicit, assessment of value as a necessary first step. Efforts by policy makers and payers to better determine the value of medicines are widespread. The 2011 AMNOG reforms in Germany and the development of "value based pricing" in the UK are two high profile examples (Runge, 2012; Department of Health, 2010) among many others (Garau and Mestre-Ferrandiz, 2009; Sussex, Towse and Devlin, 2013). HTA agencies make decisions using more or less explicit sets of criteria. None yet uses MCDA, although the European Medicines Agency (EMA) is developing an MCDA approach to balancing the benefits and risks of new medicines considered for licensing (EMA, 2012).

MCDA is a set of methods to aid decision making where more than one criterion is relevant, which make explicit the impact on the decision of all the criteria and the relative importance attached to them. MCDA is based on trades-offs between attributes: more of one attribute can compensate for less of another. The main steps are (see Devlin and Sussex (2011) for more detail) as follows.

- Establish the decision context—what is to be decided, by whom, involving which stakeholders
- Identify attributes for assessing the value of each medicine
- Assign weights to the attributes to indicate their relative importance to the decision
- Score the expected performance of each medicine against the attributes
- Combine weights and scores to provide an indication of overall value
- Consider the implications of the results and test their sensitivity to reasonable variations in weights and scores.

Variants of MCDA range from those using sophisticated algorithms to identify the total (dis-)benefits of an option, to more basic approaches limited to providing and recording a structured and explicit deliberative process. All forms of MCDA aim to achieve replicability and transparency in decision making. Replicability implies that, given a

certain set of attributes and weights, different people, or the same people on a different occasion, given the same information would make the same decision on overall value. Transparency implies that the evidence and other factors taken into account, and the decision-making process itself, are visible to outside observers. This increases the accountability of decision-makers to other interested parties. However, there might be costs of "being explicit" as developing an agreed set of attribute weights, for example, could be difficult to achieve and require time-consuming consultation processes to gain widespread support. MCDA can support decision making involving different stakeholders with non-congruent objectives, and help to resolve disputes in a structured and transparent way. MCDA has been extensively used in health care and other sectors (transport, social services, immigration policy, etc.). MCDA aids and structures the exercise of judgment by decision-makers, but does not do away with the need for that judgment (Thokala and Duenas, 2012).

OMPs are treatments for patients with rare diseases defined in Europe as conditions affecting fewer than 1 in 2,000 people. Rare diseases are often chronic, progressive and life threatening; many of them affect children and there is often a lack of effective treatments for these diseases. Small populations, substantial heterogeneity, lack of knowledge about natural history and difficulty in defining practical clinical endpoints create greater uncertainty around evidence in rare diseases than in common ones. The development of OMPs is often accompanied by partial knowledge of diseases and scarce medical expertise. Legislation has accordingly been introduced in the US and EU establishing special incentives for the development of treatments for rare diseases, and increased numbers of orphan drug designations have followed (Garau and Mestre-Ferrandiz, 2012).

Payers commonly treat OMPs differently from other medicines. A number of HTA systems have special arrangements for the assessment or reimbursement of OMPs. In England, treatments for very rare conditions are assessed and commissioned in a separate process from other treatments (until April 2013, by the Advisory Group for National Specialised Services [see AGNSS, 2012] and since then by NHS England) using criteria wider than health gains, including attributes related to societal value and impact on clinical practice. In Scotland, a special fund specifically for OMPs was set up in early 2013 (Scottish Government, 2013). At the European level, policy initiatives are aimed at improving the approach to assessing the value of new OMPs. For example, CAVOMP (EUCERD, 2012) is developing processes to inform decision makers about the clinical added value of OMPs and facilitate timely reimbursement.

Winquist, et al (2012) have proposed a process for reviewing OMPs by payers that works around problems with demonstrating clinical effectiveness. But we have not been able to find in the literature a value framework for assessing OMPs that sets clinical effectiveness alongside other attributes of value.

Launching a treatment for a hitherto untreated rare disease puts that disease on the clinical map. Clinicians are then more likely to be aware of the disease, to recognise cases that present to them, and to have the necessary skills to help (Denis, et al, 2009). This suggests that the existence of unmet need for treatment might be more important when determining the value of an OMP than when evaluating treatments of more prevalent conditions.

For all these reasons, it is important to relate the "significant benefit" value criterion required for OMP designation with a framework that, as pointed out by Hughes-Wilson, et al (2012), would allow for consistent value assessments of OMPs that potentially can be applied in different jurisdictions and across diverse rare diseases.

Our study has three aims: first, to identify and validate the list of attributes to include in the OMP value framework; second, to determine their relative importance based on the views of clinical experts and health economists who advise HTA and reimbursement bodies, and on the views of representatives of patient groups; and third, to test whether an MCDA approach can practically support decision making about the value of individual OMPs.

Methods

An initial list of value attributes for the framework was identified from a literature review of 40 rare diseases, a review of HTA for OMPs, and interviews with clinical experts, economists and representatives from rare disease patient groups. The list then was refined and validated through a series of workshops that combined and weighted the attributes using MCDA techniques.

A literature search was undertaken on the natural history and burden of 40 rare diseases (listed in Appendix A). Because over 7,000 rare diseases exist, a comprehensive literature review was impractical. A subset of 40 diseases was selected based on the availability of literature on morbidity, mortality, broader patient and carer burden, disease frequency, severity, degree of scientific understanding and progress in developing effective treatments. Searches were conducted using MEDLINE, EMBASE, the

Cochrane database, Orphanet and the EURORDIS patient association website. For each condition, disease impact was broken down by individual or group affected (patients, family, society), nature of the effect (pathological, clinical, symptomatic, outcomes, economic) and the proximity of the effect to the primary manifestation of the disease. The objective was to develop a generic rare disease burden map (see Appendix B).

A second search looked for how existing payer frameworks estimate treatment value in ten OECD countries with OMP regulatory pathways and well-established pharmaceutical reimbursement processes (Australia, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, UK and US). A related search focused on rationales given in reimbursement decisions for OMPs in those EU countries where the relevant reports were publicly available in English: the UK (NICE, SMC), France (Transparency Commission) and Germany (GBA – IQWiG). These searches were supplemented through 10 individual interviews with clinical experts, academics specialised in health economics and policy, and rare diseases patient group representatives in the EU and the US.

This process yielded an initial list of 14 attributes. Practical guides to MCDA recommend using fewer than ten attributes. We discussed the attributes at a workshop, in March 2012, with GSK managers working on the development and commercialisation of OMPs, and via aggregation reduced the list to the following eight attributes.

Impact of the rare disease and associated unmet need

1. Availability of effective treatment options / best supportive care in the absence of the new medicine
2. Disease survival prognosis with current standard of care
3. Disease morbidity and patient clinical disability with current standard of care
4. Social impact of the disease on patients' and carers' daily lives with current standard of care

Impact of using the new medicine

5. Treatment innovation, defined as the scientific advance of the new treatment together with contribution to patient outcome
6. Evidence of treatment clinical efficacy and patient clinical outcome
7. Treatment safety
8. Social impact of the treatment on patients' and carers' daily lives

The rationales for these attributes and their particular relevance in rare diseases, with references to the literature from which they are drawn, are detailed in Appendix C.

To provide a combined value assessment based on these attributes, we used an MCDA approach. We selected a "value measurement model" (7) as being of most value to HTA

and reimbursement decision makers. As this was a pilot study it was important to have the opportunity to discuss in detail with experts and rare disease patient group representatives both the attributes and how they were weighted. This implied a workshop approach, rather than a discrete choice experiment or use of "remote" tools such as "1000Minds|' (Devlin and Sussex, 2012)

Weighting of the eight value attributes listed above, and using them to rate example OMPs, were first piloted in the latter part of the March 2012 workshop with GSK managers and then formed the basis of two further workshops with:
1. Clinical and health economics experts from France, Germany, Italy, Spain and UK, in April 2012
2. Representatives of rare diseases patient groups in the EU, in August 2012.

Each of these workshops included six to eleven participants and the authors of this paper as facilitators. Additionally, medical/scientific specialists were on hand to provide factual information and clarification about the OMPs that were assessed. The workshops were highly structured and included participants working in small subgroups (three to four per subgroup) to complete tasks within strict time limits.

Following an introduction explaining the purpose and nature of MCDA and of the workshop, the first substantive session in each workshop was devoted to validating the set of value attributes. Participants at the April and August workshops were offered the opportunity to change the list of attributes agreed at the March workshop if they had concerns, but they were content to proceed using those eight attributes.

We took a societal perspective when establishing the full set of value attributes, while recognising that payers and HTA bodies in some countries currently take narrower perspectives limited to measures of clinical effectiveness or health gain (Johannesson, et al, 2009). Similarly, we asked participants when determining attributes' relative weights to take into account the interests of all relevant stakeholders including patients, their families and carers, payers and the national economy.

In the second session of each workshop, the participants assigned relative weights to the attributes via the following process. Participants were divided into small groups of three to four plus a facilitator. Before breaking into the groups, participants were asked to consider by themselves all of the attributes and to allocate each of them initially to one of three headings: "high", "medium" or "low" importance for determining the value of an

OMP. Participants then discussed in their small groups how to allocate 100 weighting points across the eight attributes. Each group reached a consensus weight out of 100 for each criterion. The individual groups' weightings then were reported to a plenary session, any significant differences between groups' weightings were discussed and each group was given the opportunity to revise its weightings. It always proved possible in the plenary discussion to reach a consensus weighting for each attribute: all participants were content to accept an average of the groups' individual weightings, as amended following the plenary discussion, where there was any difference in those weightings.

An important part of the study was to test the views of rare disease patient groups, clinical experts and health economists about the balance of weights between the two groups of attributes: those related to the disease being treated and those concerning the effectiveness of the new medicine at treating the disease. Empirical studies support the use of the severity of the disease being tackled as a criterion for determining the value of a treatment, although the exact strength of that support is less clear (Shah, 2009). There is less evidence about the importance of unmet need *per se* although what little there is does suggest that it is a relevant factor (Green and Gerard, 2009).

After establishing the attributes' weights, the workshop participants were asked to rate two case study OMPs against the criteria. Participants had been provided before the workshop with concise briefs, written in non-technical language, describing the nature of the disease being treated and its impact on patients and carers, and the evidence about the characteristics and impacts of treatment with the medicine based on available clinical data. Medical/scientific experts on the case study medicines were available to provide factual answers to any questions of clarification from participants.

As with the weighting exercise, participants were given time to rate by themselves each new treatment against each attribute before going into the same small discussion groups as before. The rating scale ranged from 1 = worst score to 7 = best; participants were required to allocate only whole number scores, not fractions or decimal places. The 1–7 scale was chosen to permit sufficient discrimination without introducing an inappropriate impression of precision. Points 1 to 7 on the scale for each attribute were defined so that a higher score always indicated "better" as per the definitions provided in Appendix D. Then, in the small groups, the rating of each treatment was discussed briefly in turn for each attribute. A commensurate process to that for the weighting task was followed, with consensus scores for each case study OMP against each of the criteria being agreed in a plenary discussion.

In the final workshop, session participants compared the overall value scores of the two OMPs (which was given by the sum of the weighted scores) and the key attributes driving the score in each case. Aided by an expository Excel-based tool developed for the project, sensitivity analyses were conducted in "real time" in front of the workshop participants, based on combinations of adjustments to relative weightings of criteria and to scorings against each criterion, within the ranges of weights and values that had been discussed in the respective earlier plenary sessions. In addition, comparing the weighted scores of the two case study OMPs enabled the participants to ensure that they were satisfied with the reasons for the apparent differences between the two medicines' overall values. This is an important aid to ensuring consistency between value assessments, which taking an explicit MCDA approach makes possible.

Results

We report the outcomes of the two workshops with participants invited by, but external to GSK, namely a group of European clinical and health economics experts at the April workshop, and a group of European rare disease patient group representatives at the August workshop. The results of this study are presented as "proof of concept" rather than as definitive values. Different groups, with different perspectives, could reach different views on the attributes' weights, i.e. on which were the more/less important value attributes.

Both workshops proved successful as pilots of the MCDA process. All participants proved able and willing to engage with the tasks in all sessions of the workshop and a consensus was agreed with respect to criteria weightings and to the scoring of case study medicines in terms of those criteria.

Table 1 summarises the attribute weights produced by the "experts" and "patients" workshops, respectively. The clinical experts and health economists considered that the most important attribute was evidence of impact on patient outcomes, which attracted 28% of the total weighting. The next most important criterion was, perhaps more surprisingly, the extent to which there is currently an alternative treatment, which was given a 19% weighting. Taken together, these two top criteria account for almost half (47%) of the total weighting. The clinical and health economics experts decided to accord no weight to whether development of the medicine brought a scientific advance, with the stated rationale that when the other seven attributes are taken into account, this attribute would not be seen as adding any further value by patients and carers or by health care payers.

Table 1: Criteria weights (%) from two workshops

Per cent	"Experts" workshop	"Patients" workshop
Availability of existing treatments	19.5	11.0
Disease survival prognosis with current soc	14.0	11.5
Disease morbidity and patient clinical disability with current soc	12.0	15.0
Social impact of disease on patients' and carers' daily lives with current soc	8.0	15.0
Sub-total weight for impact of disease / extent of unmet need	*53.5*	*52.5*
Treatment innovation: scientific advance + contribution to patient outcome	0	5
Evidence of treatment clinical efficacy and patient clinical outcome	27.5	17.5
Treatment safety	8.0	7.5
Social impact of treatment on patients' and carers' daily lives	11.0	17.5
Sub-total weight for impact of new medicine	*46.5*	*47.5*
Total	*100.0*	*100.0*

Key: soc = current standard of care

The rare disease patient group representatives in their workshop differed from the clinical and health economic experts in some aspects of the weightings (see Table 1). In general the patient group representatives spread the weights more equally across the eight value attributes. The patient group representatives gave more weight than the clinicians/economists to the impact of the disease, and of the new treatment, on individual patients' and carers' daily lives; and also were willing to give some weight (5%) to treatment innovation/scientific advance. The (un-)availability of existing treatments was less important to the patient representatives than it was to the clinicians/economists. So, too, was evidence of treatment clinical efficacy and patient clinical outcome, although this remained the (equal) most important criterion, as it had been for the clinicians/economists.

Overall, both sets of workshop participants agreed, independently of one another, to give slightly more weight to the attributes of the disease being targeted than to the impact of the new medicine aimed at it: around 53% versus 47%. This result was explicitly discussed in the plenary session at each workshop and each time was confirmed as the collectively desired balance.

Two case study OMPs in the GSK pipeline were scored at the workshops for the extent of their achievement of the eight attributes, with the help of factual clarifications by experts in the disease areas concerned. To ensure a robust test of the MCDA process we selected two example OMPs with clearly differentiated profiles, as described in Table 2.

Table 2: Profiles of the two OMPs rated in the MCDA workshops

Value attribute	Treatment A	Treatment B
Availability of effective existing treatment options	Yes	No
Main target patient outcome	Survival	Progression of disease
Therapeutic area	Immuno deficiency	Neuromuscular
Prevalent population range in EU	250-600 patients	3,000-8,000 patients
Pivotal trial–data package	Open clinical trial (no control group)	Randomized double blind placebo controlled

The overall result each time was that the same medicine emerged as considerably more valuable than the other, although not on every one of the criteria. The higher value medicine was seen to be so mainly because of the greater benefits achieved by the treatment, rather than major differences in disease impact without treatment. The process made explicit, across all workshops, the trade-offs made between different value attributes in reaching the overall assessment of value for each case study OMP. -For each attribute, workshop participants were able to discriminate between factors they thought did or did not impact value of treatment. Sensitivity analysis showed that only with implausibly large changes to attributes' weights would the ranking of the two case study medicines change. The medicine deemed of higher value using the framework was judged by the workshop participants to be so mainly because of greater benefits from the treatment rather than major differences in disease severity or unmet need between the two case studies.

Limitations of the study and further research

Our MCDA approach has limitations. Ours was a pilot study with small numbers of selected experts and patient group representatives taking part. There is certainly scope for more research involving larger samples. But the patient group representatives in our workshops represented a diverse range of rare diseases and all had experience at national and/or supranational levels of informing rare diseases policy. The clinical and health economics experts all had practical experience of informing payers and policy-makers at national and/or supranational levels about rare disease value assessment. Any MCDA process based on workshops of limited scale and duration may be criticised for superficiality, but arguably HTA and pricing and reimbursement committees suffer equally in this regard. Pragmatism dictates the time and resource limits in all cases. None of the participants in our workshops expressed unwillingness to agree and weight value attributes within those constraints.

An interesting result was the differences between the weights agreed in the two workshops. To produce a single consensus set of weights would be an interesting focus for future research. Given the willingness of all participants within each workshop to listen to others' views and arguments, to compromise and to agree, we are confident that adding a further stage to the process—where, for example, the results from the two sets of participants were brought to a combined plenary meeting of all participants—would be likely to yield a mutually acceptable set of weights.

Further research focusing on understanding the extent to which the value attributes and their weights for OMPs differ from those for treatments of more prevalent diseases also would be valuable.

Discussion

Our MCDA approach and specific OMP value framework provide a useful tool that might fit in real-setting decision making in different ways. In countries where separate processes for OMPs already exist, our MCDA tool can be applied to enhance transparency and consistency of decision making and ensure that all relevant elements of value of OMPs are taken into account. In the long term, it might become possible to conduct a common, pan-European, non-financial assessment of the value of OMPs (which would leave reimbursement as a country-level decision) in the spirit of the on-going initiatives in the European policy arena (EUCERD, 2012).

Our framework and MCDA tool could provide a starting point for the development of such a decision making process. Development could involve further validation of the value attributes included in the framework, for example by running multiple focus groups involving a broader range of participants with different health status, socio-demographic characteristics and nationality.

Our study revealed differences between "experts" and patient group representatives' views of the relative importance of some attributes. Patient group representatives' placed greater emphasis on quality-of-life aspects, with and without treatment, for patients and those around them: the people they represent may be more concerned than the experts assume with the subjective quality of their lives than with more objective clinical measures of outcome. Patient group representatives also were less concerned than the experts about the unavailability of existing treatments, *per se*, independently of what that meant for quality and length of life. It will be important in future research to test the significance or otherwise of these apparent differences.

It also will be important to elicit attributes' weights from groups beyond experts and patient group representatives; alternative methodologies such as discrete choice experiments could be used. Estimating attributes' weights across countries will reveal how far preferences over treatment characteristics vary across health care payers and systems.

The identification of the best form of MCDA remains an empirical question. There is a continuum of approaches ranging from algorithmic methods to more deliberative processes that allow for exceptions to be made. Each approach has advantages and disadvantages. Decision-makers understandably may be reluctant to submit themselves to public scrutiny, but excessive secrecy damages public confidence in the decisions of HTA and reimbursement bodies. MCDA approaches increase the defensibility of decisions. Therefore, on balance, we believe that a possible way forward is using an MCDA tool to inform decision-makers' deliberative processes, rather than it being applied in a mechanistic way.

The aim of our study was to provide a framework to measure and value non-monetary attributes of OMPs. Decision-making processes involve an additional step, which is the comparison of benefits with costs to determine price, reimbursement status and/or recommended use within a health care system. This would involve a mapping of willingness to pay by each payer/decision-maker onto the value of OMPs as measured by the agreed framework. However, this aspect is beyond the scope of our study.

Conclusions

A value framework for OMPs was constructed from literature reviews and interviews. The resulting set of eight attributes covered the nature of the disease being treated as well as the effects of the treatment being considered. The value-measurement model, workshop-based, MCDA process proved practical in pilots. Participants in the workshops were able and willing to agree attribute weights and how well exemplar medicines achieved the attributes. The clinical and health economics experts and patient group representatives were able to discriminate between attributes, and to develop a shared understanding of the issues and a clear articulation of value trade-offs. Participants unanimously confirmed that the MCDA approach provided clarity, logic and transparency. Given the intrinsically complex nature of the rare diseases and OMPs environment, an MCDA approach for rare disease treatment value assessment has the merit of ensuring shared understanding of the elements of value as well as a clear articulation of trade-offs between those elements. The MCDA approach and resultant value framework are complementary with current EU policies on OMPs. An OMP value framework derived via MCDA offers a possible construct for more comprehensive guidance to HTA and pricing and reimbursement decision making.

Appendix A: The 40 diseases included in the literature review

Adenosine deaminase deficient severe combined immunodeficiency (ADA SCID)

Acute graft-versus-host disease (aGVHD)

ALS no go

Alternating hemiplegia

Aniridia

Ataxia

ATTR amyloidosis

Chromosome 11 disorders

Churg Strauss

Congenital ichthyosis

Crohn's disease

Cystic fibrosis

Cystinosis

Duchenne muscular dystrophy

Ehlers Danlos syndrome

Epidermolysis bullosa

Fabry disease

Fragile X syndrome

Gaucher disease

Hereditary tyrosinemia type 1

Homozygous familial hypercholesterolemia (HoFH)

Huntington's disease

Hypophosphatasia (HPP)

Marfan syndrome

Metachromatic leukodystrophy (MLD)

Mucopolysaccharidosis (MPS) I

Mucopolysaccharidosis (MPS) II

Mucopolysaccharidosis (MPS) VI

Myasthenia gravis

Niemann-Pick C

Osteogenisis imperfecta

Pompe disease

PraderWilli syndrome

Pulmonary arterial hypertension

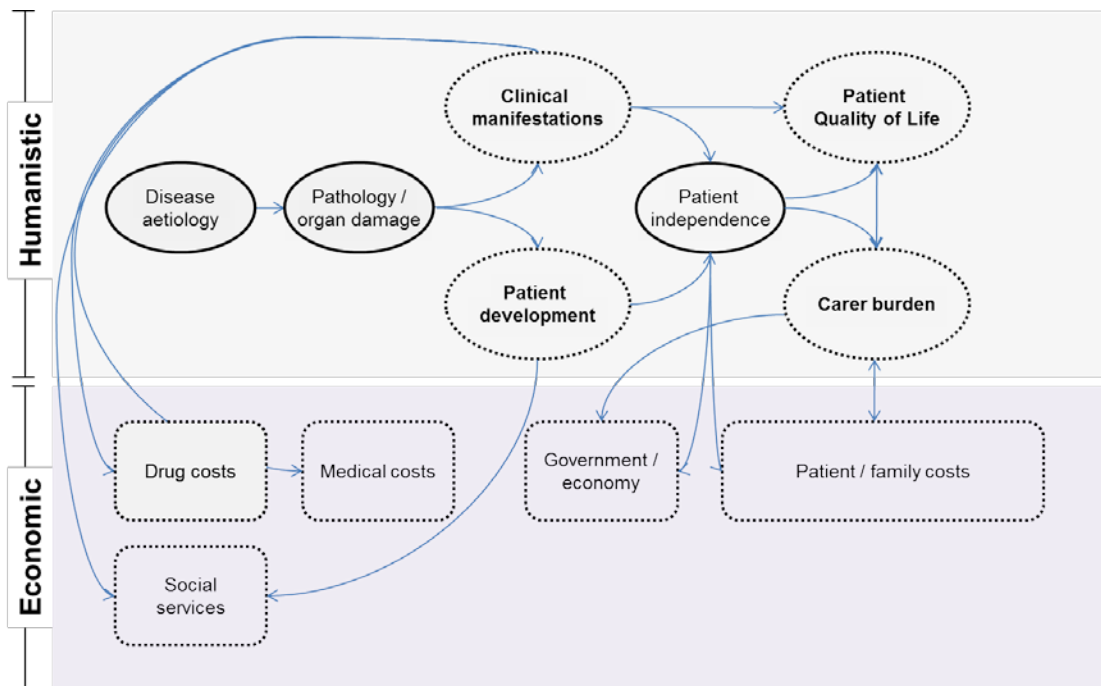Retinitis pigmentosa

Short bowel syndrome

Transfusional iron overload

Tuberous sclerosis

Urea cycle disorders

Williams syndrome

Appendix B: Disease burden road map

Appendix C: Rationale and relevance of the eight value attributes for rare diseases

Value attribute	Rationale and relevance in rare diseases (references listed below table)
1. Availability of effective treatment options	A patient association survey of 18 rare diseases identified the absence of treatment options as a major issue in rare diseases (1). Of the 40 diseases included in the literature review, only 10 had a drug specifically approved by the European Medicine Agency (EMA), and 2 more diseases had a licensed drug therapy approved by the FDA. Non-pharmaceutical disease management alternatives, such as transplantations, speech therapy, orthopaedic surgery, and physiotherapy are frequently used to relieve patients' symptoms and disabilities in more than one disease in two.
2. Survival prognosis	The impact of premature mortality is consistently documented in the sample of rare diseases included in this review. In more than three-quarters of the diseases, investigated patients were expected to have reduced life expectancy (1,2,3,4,5,6,7,8,9). In a quarter of the diseases, life expectancy was reduced by more than 20 years and in 17% death was expected before adulthood (1,2,3,5,6,7,8).
3. Morbidity-disability	The two most important clinical complications observed in the selected sample were patient physical and cognitive impairment in combination with the multiplicity and the severity of the symptoms (4,9,10,11,12). Patients were often affected by multiple symptoms as a result of the disease affecting more than one organ class. Multiple organ systems were identified in 76% of the diseases reviewed (3,4,6,10,12,13,14,15,16).
	Physical impairment included enlarged organs such as the spleen and liver, muscle wastage, spinal damage, cardiovascular disease, renal disease and constricted respiratory function (4,6,14, 17). Pain was present in many of the diseases, with significant physical pain being recognised as a symptom in 43% of the sample (13,18,19,20,21,22). In addition to physical impairment, 43% of the diseases studied affected patient cognitive function (2,10,11,12,23).
	In paediatric patients, growth disorders were observed in 49% of the diseases, including short stature and skeletal deformity (6,8,12,14, 20,22,24,25,26). Developmental impairment was also present in 46% of the diseases and included learning disabilities, mental retardation, speech problems, attention deficit and difficulties in forming social relationships (10,12,14,16,23).
	The severity of the symptoms was of particular importance. In many of the conditions the physical impact of the disease leads to disability, with 40% of the diseases leaving patients dependent on assistance in all activities and 20% of patients requiring a wheelchair or walking aid (12,19,20,27,28,29,30).
4. Social impact of disease on patients' and carers' daily	The impact seen amongst the sample of rare diseases also extended to significant social impact.
	Social impact is first characterized by reduced loss of patient autonomy and independence. In some diseases basic daily functional tasks such as talking, swallowing, or going to the toilet without assistance became

Value attribute	Rationale and relevance in rare diseases (references listed below table)
lives	problematic (1,12,23). In other diseases, more advanced activities such as working, studying, travelling or playing sports were often restricted (1,29,31). In 40% of diseases there was a need to adapt patients' homes and work environments to accommodate their disability (20,32).
	A second characteristic of rare diseases social impact is the psycho-social burden imposed by disease clinical conditions. Thus in 57% of the diseases, patients were reported to demonstrate increased stress, anxiety, depression and loneliness (18,29,33,34,35,36). The psychological burden was linked to morbidity, pain, social exclusion and the expectation of an early death (31).
	In addition, members of families with patients with rare diseases and their carers are also affected (24,27,30,37,38,39,40). Within this sample, the loss of parental independence was also recorded in 57% of the diseases, with parents or carers having their daily activities restricted due to caregiving responsibilities (18,24,27,30,38,41).
5. Treatment innovation	There is some debate about the relevance of assessing the innovation associated with a new drug when establishing treatment value (42,43,44). The definition of innovation in this context is not well established. However, some international payers – most notably in Italy, Japan and US (45,46,47) – consider innovation to be a central consideration when deriving drug value (46,48,49,50).
	Treatment innovation is defined in this framework as magnitude of the scientific advancement of the new treatment and its contribution to patient outcome.
6. Evidence of treatment clinical efficacy and patient clinical outcome	Treatment clinical efficacy is a fundamental element of importance within a value framework. It is the single most important element of treatment value within existing pricing and reimbursement systems. All payer systems reviewed in this study incorporated some form of measure of therapeutic benefit in the drug assessment process, however they differed in how they construed benefit (51,52,53,54).
	The context of the disease, its rarity and implications for the quality of the clinical data package are important. Disease rarity creates uncertainty around clinical data, however it is still possible to conduct robust clinical programmes, even with small sample sizes (55,56). The lack of established surrogate endpoints in rare diseases increases the importance of establishing relevant patient outcomes from treatment (57). The proposed framework therefore assesses the potential for a given drug to modify patient outcome over the course and progression of disease as well as reducing its clinical signs and symptoms.
7. Treatment clinical safety	Drug safety and tolerability profiles are considered important factors when assessing treatment value. All the pricing and reimbursement systems reviewed in this study incorporated assessment of the safety profiles of new treatments (51,52,54,58). In Germany, for example, IQWiG assessments place emphasis on safety, and drugs have had their benefit rating downgraded by the agency as a result of perceived safety issues.
	Many payers consider the side effect profile relative to the severity of the disease and the benefit from treatment. In France, the Transparency

Value attribute	Rationale and relevance in rare diseases (references listed below table)
	Committee explicitly estimates a benefit/risk ratio as part of the assessment of a new drug, at the same time as it considers the severity of the disease (51). In rare diseases, the severity of the conditions and the absence of existing treatments have meant that patients and carers are keen to play a role in determining the relative weights to be allocated to consideration of what constitutes acceptable risks and worthwhile benefits (59).
8. Social impact of the treatment improvement on patients' and carers' daily lives	As described in Attribute 4, the burden of rare diseases falls beyond patients, and impacts carers, families and wider society. Given the lack of formal data on these elements in many rare diseases, both objective and subjective measures of value are relevant in understanding benefit, including patient and carer testimony. Findings from our review of the disease literature document the importance of the humanistic and psychosocial burden incurred by families and carers in rare diseases (60,60). These findings are also consistent with patient surveys in rare diseases (1,59).

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Appendix D: Definitions of attributes included in the value framework for OMPs

Domain	Value attribute	Definition
Rare disease unmet need	1. Availability of effective treatment options	<u>Is there a treatment as standard of care and how effective is it?</u> (From no medical treatment available or palliative care only <u>to</u> cure/disease modifier treatment available)
	2. Survival prognosis	<u>What are the disease markers of premature mortality?</u> (Survival prognosis from diagnosis; <u>or</u> age of death)
	3. Morbidity-disability	<u>What are the clinical manifestations and complications of the disease:</u> severity of handicap over the lifetime duration of disease <u>or</u> chronicity and duration of disorders <u>or</u> age of onset of morbidity?
	4. Disease social daily living impact (patient and carer)	<u>What is social impact of the disease defined as:</u> autonomy & independence of patient/carer psychosocial/emotional impact for patient/carer magnitude of impact on social daily activity & life style impairment (patient & carer)?
Medicine Therapeutic Benefit	5. Treatment innovativeness	<u>What is the degree of scientific innovation provided by the treatment defined as:</u> R&D intensity associated with the manufacturing process, technology, mechanism, formulation its contribution to patient care (outcome)
	6. Treatment clinical efficacy & patient outcome	<u>How clinically meaningful are treatment efficacy results?</u> quality of data package / data uncertainty in context of disease rarity magnitude of clinical improvement /patient response in clinical trials (pivotal study mainly) magnitude of the impact of the treatment on disease progression & patient outcome improvement
	7. Treatment clinical safety	<u>What are the severity and frequency of side effects?</u>
	8 .Treatment improvement on social daily living	<u>What is the treatment social impact , defined as:</u> impact on autonomy & independence (patient/carer) psychosocial/emotional impact impact on social daily activity & life style impairment (patient/carer)?

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