Limits on use of health economic assessments for rare diseases

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Summary

Funding of expensive treatments for rare (orphan) diseases is contentious. These agents fare poorly on ‘efficiency’ or health economic measures, such as the quality-adjusted life years, because of high cost and frequently poor gains in quality of life and survival. We show that cost-effectiveness assessments are flawed, and have only a limited role to play in reimbursement decisions for orphan drugs and beyond.

Introduction

Should European Union (EU) governments accommodate expensive treatments for rare, ‘orphan’ diseases within strained healthcare budgets? The question is a tense one.

The opportunity cost is substantial. Some argue that for example £2.5 million spent on orphan drugs (say 15 patient-treatment-years at £160,000 annually) would pay for over 520 hip replacements.1 It is argued that financing decisions should be based at least in part on health economic/technology assessments (HTAs)1,2 on which orphan drugs fare poorly for reasons explained below and would probably not be financed. For example the Netherlands has questioned whether treatment for Fabry and Pompe diseases, costing up to €200,000 and €700,000 per patient per year, respectively, should be fully reimbursed.3

At the same time, access to orphan drugs remains limited, and the EU wants to remedy the problem.4 A tailored funding assessment may therefore be appropriate. A European working group has recommended a preliminary assessment matrix for optional use by EU Member States to harmonize access to orphan therapies, incorporating as one factor cost-effectiveness (though there is no consensus as to how to convert the matrix into a numerical formula for funding decision-making).5 Some Member States have followed suit: for example the UK has announced that ‘very high cost’ orphan treatments will be assessed separately by the National Institute for Health and Clinical Excellence (NICE), which will devise a ‘robust, independent and transparent’ mechanism for the commissioning of orphan products.6 Other ‘urgent’ calls for revised reimbursement criteria have generated proposals to focus e.g. on disease severity and manufacturing complexity.7,8

This article informs this debate. We highlight below important limitations of cost-effectiveness approaches which public and private health providers must bear in mind when devising reimbursement criteria. We focus on the UK healthcare system with which we are familiar. We also refer briefly to our argument made elsewhere that from a moral perspective the better basis for making treatment
Root of cost-efficiency: utilitarianism

A central characteristic of cost-efficiency arguments is that they stem from utilitarianism. Utilitarian principles dictate that the morally correct outcome must be calculated: the outcome which generates the 'most utility' is the morally right one.\(^9\)

Utilitarianism is popular with those who regulate provision of health because it is easy to understand (greatest good for the greatest number); it is particularly attractive to those who want to compare health gain for treatments used in diverse groups of patients. A common yardstick in England is the quality-adjusted life years (QALY).\(^11\) It is used by NICE to recommend how to prioritize treatments within and between patient groups\(^12\) by applying a cost threshold per QALY. There are other metrics: for example the disability-adjusted life years (DALY) is accepted internationally. Given its popularity in the UK, we focus here on the QALY.

Redeemable limitations of cost-effectiveness formulae

Standard HTAs are difficult in the orphan context because often an orphan therapy is the first treatment of its kind and no comparison with similar therapies is possible (though they may be compared with e.g. surgical alternatives), or data are lacking to permit an appraisal of outcomes. These aside, the QALY-metric itself has several additional limitations:

1. **Arbitrary cost-threshold and inflation**: A price ceiling has been set at £30 000 per QALY in the UK,\(^13\) although NICE has come to lower the ceiling to £20 000 for most conditions.\(^14\) The threshold is arbitrary and historically based on the cost of haemodialysis in the 1970s;\(^15\) it has not been changed since NICE was launched in 1999 and is thus out of step with inflation.\(^16\)

2. **Opaque and age-discriminatory calculus**: NICE’s economic model is viewed as a ‘black box’, the results of which external parties have been unable to verify.\(^16\) The application of utilitarian approaches to rare diseases and beyond is generally thought ‘crude’.\(^17,18\) The QALY is also ageist in that it prefers treatment of the young who are likely to survive longer.\(^9\) Similarly, the DALY measures human productive capacity and can value young adults more highly than the life of children and the elderly.\(^19\) The EU working group recognizes that its matrix, too, requires work before it can function as a transparent mathematical model.\(^5\) This may explain why the Medicare system (the largest US insurer which covers nearly all over 65-year-olds and disabled Americans) is prohibited by law from using cost-effectiveness analysis for treatment decisions.\(^20\)

3. **Limited inputs**: The QALY’s range of inputs is too narrow. In particular, for long-term outcomes, the formula fails to take into account savings generated by early treatment, which may pre-empt—in the example of Type 1 Gaucher’s disease—costly blood transfusions, splenectomy, analgesia, frequent hospitalization and joint replacement surgeries later in life. Whilst individually considered cost-effective, over an untreated patient’s lifetime these procedures can be very costly for the health system; splenectomy appears to worsen long-term outlook and disability by increasing the risk of osteonecrosis. QALY also ignore the economic benefit of early and effective treatment, which can allow the patient and their family to participate in working life. An example is a young married professional diagnosed with Type 1 Gaucher in his early twenties who, treated with enzyme replacement therapy, with his wife makes tax contributions nearing £100 000 per annum. This covers the cost of the drug without which his wife might not be able to work outside the home, as is often the case. We do not suggest that tax contributions and savings on care should determine whether an individual patient is treated, or that all patients make tax contributions at this level or that all orphan drugs are priced as highly, but only wish to highlight the savings that can be generated by effective treatment. These savings are also missing from the EU working group’s proposal.\(^5\)

4. **Societal value**: The UK has proposed a weighting of ‘societal value’ as part of a funding assessment.\(^21\) Such values might include equal opportunity, fairness and diversity but some have used this notion to argue against treating those affected by rare diseases, as rarity is not valued by society. We rebut this robustly below and show that equality of opportunity should be the paramount consideration in determining social value (see ‘Alternative analysis’ and ‘Potential objections’ sections).

5. **Blind to prejudice and time inconsistency bias**: Finally, the QALY is blind to historical prejudice. Orphan therapies can be labelled as ‘cost-ineffective’, and lack long-term data on safety and effectiveness relative to more researched conditions because orphan conditions have often not benefited from decades of research. They are also ‘expensive’ because of the laudable legislative incentive schemes to remedy this problem: EC Regulation 141/2000 bestows inter alia a 10-year marketing exclusivity to allow manufacturers to recoup the cost of developing and marketing orphan drugs. Orphan therapies’ cost and efficacy are therefore morally arbitrary, and taking them at face value risks jeopardising the incentives bestowed by the European Parliament. There is also a time inconsistency bias, meaning that preferences can change over time: when transplants were first introduced they faced resistance as radical and expensive, but are now standard practice.
Indeed, what is often ignored is that we make exemptions in other fields of medicine where society is evidently reluctant to price human health. Transplant operations tend not to be sacrificed on cost-efficiency grounds even though the recipients have a reduced life expectancy and high ongoing cost of maintenance of immuno-suppression and treatment for other complications. We can be similarly hesitant even where lives are not at stake: it would be unthinkable to propose limiting access to the British Museum for the disabled due to cost of stair-lifts or elevators for wheelchair users, or to apply a QALY-metric to see if such access is cost-effective. No sound distinction can be drawn between a wheelchair-bound patient whose disability may never improve, and a patient with an orphan disease whose treatment only stabilizes their clinical condition and does not reverse it, though many orphan drugs show strong efficacy.

Irredeemable limitations of cost-effectiveness formulae

Although some of the above shortcomings are remediable by redesigning the metric, four further philosophical problems with health economic approaches render them categorically unsuitable as a sole basis for deciding whether to fund a treatment—rare or common.

1. **Valuing the quality of another’s life:** Health economics presumes that it can accurately value the quality of another person’s life, on average. This assumption is fraught with difficulty on an individual basis; humans are poor judges of other’s quality of life.

2. **Degrading human life:** Expressing a person’s health, quantity and quality of life in readily comparative economic units, thus placing a price on human life, arguably degrades and diminishes the personal integrity and objectifies humans.

3. **Humans as locations of utility:** Utilitarianism does not take serious account of pain and suffering and regards humans merely as ‘locations’ for units of utility (or health). This focus on end states rather than persons is evident in statements such as ‘reimbursement [of orphan drugs] would generate a decrease in population health that is larger than the improvement in the outcomes of patients using the orphan drug’. One consequence of this focus is that QALY do not take into account the relative safety of treatments: a QALY analysis would favour bone marrow transplantation for Gaucher disease, which can be fatal, rather than safe and effective enzyme infusions. Based on QALY cost, NICE should have opted for risky bone marrow transplantation over cerelzyme for Gaucher disease (with a cost of between £380 000 to £476 000 per QALY, depending on genotype). NICE however recommended the latter, departing from a pure cost-effectiveness approach.

4. **Cost is morally arbitrary:** Finally, many health prioritization debates take the form ‘Anna and Ben each need 100 ml of a drug to live and Celia needs 200 ml. Should we treat Anna and Ben, or Celia?’ We argued in point (5) earlier that orphan therapies’ cost and efficacy is the result of historical accidents and events. As a result, orphan drugs’ cost and efficacy could be given a compensatory weighting in a health assessment formula. But our conundrum about Anna, Ben and Celia shows that the problem is more fundamental: for many if not all life-saving therapies, the effective dosage and its cost are from a patient’s perspective morally arbitrary—they have done nothing to affect how much of a drug they need, or how much that drug costs. Arguably the only relevant question is: regardless of cost and dosage, does the drug improve health or stabilize this patient’s disease manifestations?

If the answer is yes, the drug should be covered for Anna, Ben and Celia. One objection is that this would lead to bottomless healthcare spend, and we deal with this objection elsewhere (Hyry et al., Orphan drugs, expensive yet necessary, in submission).

Alternative analysis

Given these limitations, we argue that in a fair society, HTAs cannot be deployed when the choice is between treatment and no treatment (Hyry et al., Orphan drugs, expensive yet necessary, in submission). This is because failure to provide treatment would deny an individual the right to pursue their life plan. Cost-efficiency calculations moreover cannot be used to prioritize among or between different patients and patient groups, for example between Gaucher’s disease and diabetes mellitus, both metabolic disorders. This is because from a fairness perspective, one person’s equal opportunities and liberties cannot be sacrificed for another’s (Hyry et al., Orphan drugs, expensive yet necessary, in submission).

However, a well thought-through cost-efficiency calculation may have an important place in the distribution of healthcare resources in cases where a patient (or prescribing physician) has a choice between two or more equally safe and effective treatments (Hyry et al., Orphan drugs, expensive yet necessary, in submission). There are for example five orphan drugs for primary pulmonary hypertension, at least one of which also has a non-orphan indication. Here a comparative-effectiveness assessment is a practical solution to reducing costs, as a person’s only chance at equal opportunity is not at stake (Hyry et al., Orphan drugs, expensive yet necessary, in submission). More generally, scholars of health economics have advocated for the
importance of comparative-effectiveness research in more efficiently allocating health resources—in particular in situations where it may be infeasible to use cost-efficacy as a decision metric. To this end, we recommend a metric that is developed transparently and through continued roundtable cooperation of patients, other tax payers, industry, insurance and EU governments with the above factors in mind, bearing in mind legal arguments which demand providing these treatments.

### Potential objections

**Orphan drugs not sufficiently ‘special’ to justify high cost**

One view is that, because orphan drugs often ‘cost more’ than more common drugs and can ‘display lower clinical efficacy’, they must have a ‘special’ redeeming feature such as ‘disease gravity’ that justifies their funding over more common diseases which are subject to standard HTAs.

They are in fact ‘special’: the EU has chosen rare diseases as one of its ‘priorities’ given the historic neglect.

Further, the focus on orphan drugs’ cost and low efficacy repeats in a disguised but detrimental way the historical prejudice against rare diseases (see point (5)):

- Orphan drugs can ‘cost more’ than therapies for common drugs because patients affected by rare diseases historically had no access to treatment and died prematurely. The EU therefore deliberately designed an incentive scheme to increase the supply of orphan therapies. This often generated effective treatments, which were acknowledged to cost more so that manufacturers could reap back the investment.
- Often ‘low efficacy’ is a result of these life-saving treatments being relatively new: they have not benefited from decades or high volumes of research as has been the case for many more common diseases.

Denying treatment on the basis of high cost and low efficacy therefore rejects treating patients suffering from rare diseases ‘because their disease is rare’. This arguably contravenes disability legislation, as well as EC Regulation 141/2000 which holds that ‘patients suffering from rare conditions should be entitled to the same quality of treatment as other patients’.

The justification for tolerating the high cost and low efficacy of orphan treatments is not that they have unique features. The true reason is ‘equality’ in health outcomes: we want to keep alive, and improve the health, of those who suffer from debilitating and life-threatening diseases, whether rare or common (Hyry et al., Orphan drugs, expensive yet necessary, in submission).

### Rejected by ‘society’

A related argument is that because orphan drugs lack ‘special’ status, ‘society’ has rejected their funding. The proponents of this view may point to the deliberations of NICE’s Citizen’s Council and a poll of a random sample of citizens in Norway which appear to show that the majority view does not support the provision of these expensive drugs.

However, orphan drug enactments, human rights and disability legislation in the EU and beyond are drawn up and ratified by parliaments representing a ‘majority’ of each population and therefore amount to a society’s legal expression that rarity is to be valued. When the EU pronounced orphan diseases a priority, it too acted as the EU’s voice.

Further, survey-based approaches are inherently biased. Those participating in a study approach the question from their particular position in society: their and their family’s health and wealth. But because the aim of these studies, and the aim of health allocation, is a ‘fair’ distribution, we need to approach the question as neutrally as possible; the same is true for HTAs which seek to quantify ‘societal impact’ or ‘societal value’.

We propose to arrive at a fair distribution by designing a society’s funding policies from behind a ‘veil of ignorance’: we do not know whether we will end up being healthy or wealthy in the society we are creating. As a result, we will design a society in which one will fare well even when affected by a debilitating or life-threatening disease. We discuss the resulting ‘just society’ elsewhere (Hyry et al., Orphan drugs, expensive yet necessary, in submission).

### Conclusion

Those who suffer from treatable rare diseases have become a public symbol of perceived fiscal excess in modern medicine. Arguments to deny their funding based on cost and low efficacy or efficiency are superficially attractive. But finger-pointing and flawed arguments clearly should be resisted. Careful examination shows that health economic approaches are limited in several important ways and inadequate as the sole basis for making decisions about treatment but, if appropriately devised, will have targeted use in the orphan disease context and beyond—in particular, in cases where comparative-effectiveness research can be applied to
improve cost-efficiency without sacrificing the best chances of patients who are ill.

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