Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers

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ABSTRACT

We find ourselves in an era of unprecedented growth in the development and use of so-called “orphan” drugs to treat rare diseases, which are poised to represent more than one-fifth of pharmaceutical expenditures by 2022. This widespread use has been facilitated by legislative and regulatory incentives in both the United States and abroad, yet US payers and health systems have not yet made a concerted effort to understand whether and how rare diseases require special considerations on their part and how to adapt traditional methods of health technology assessment and economic evaluation to accommodate these situations. In this article, we explore the general ethical dilemmas that rare diseases present, steps taken by health technology assessment bodies worldwide to define the level of rarity that would necessitate special measures and the modifications to their assessment and valuation processes needed, and the contextual components for rare-disease evaluation that lie outside of the assessment framework as a guide to US decision makers on constructing a formal and relevant process statewide.

Keywords: orphan drug production, rare diseases, neglected diseases, orphan diseases, economics, financing

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Introduction

The National Organization for Rare Diseases estimates that approximately 30 million Americans are affected by one of 7,000 rare diseases, typically defined as affecting fewer than 200,000 individuals, or approximately 60 per 100,000 population [1]. Biopharmaceutical products targeted at these rare conditions are often called “orphan drugs.” In recent years, approval of orphan drugs for serious, disabling, and often rapidly fatal diseases such as cystic fibrosis, dystrophic syndromes, and certain cancers such as lymphoma and melanoma have improved prognosis and provided new hope to patients with few or no existing treatment options [2].

Following on these successes, the market for orphan drugs is in a period of significant acceleration. Worldwide sales of orphan drugs first reached $100 billion in 2015 but are expected to more than double by 2022 and will represent more than one-fifth of all prescription drug sales by that time [3]. One factor driving the trend in spending on orphan drugs has been higher acquisition cost. A recent estimate that considered publicly available prices before insurer rebates or discounts calculated an average annual cost for orphan drugs that is five times higher than for non-orphan medications ($140,443 vs. $27,756, respectively) [3].

Historically, higher prices for orphan drugs have not been associated with greater barriers to insurance coverage in the United States, in part because it was widely recognized by insurers that even very high prices, when multiplied by small patient numbers, would produce a limited impact on budgets and insurance premiums. In addition, there has been a general sense that what can be termed “orphan prices” needed to be high per patient for innovators to make a reasonable profit after recouping research and development costs. Both considerations are subject to great uncertainty, however. First, there is no universal agreed definition of what constitutes a “rare” disease. A recent survey of definitions from more than 1,100 organizations worldwide found significant variation, ranging from prevalence thresholds of five to 76 cases per 100,000 population [4]. Variation was correlated with stakeholder type, with patient groups and payers employing the most liberal and restrictive definitions, respectively. In addition, there is no clear threshold for what a “reasonable” innovator profit might be, a discussion further complicated by the presence of government subsidies for orphan drug development that offset significant clinical development costs, provide tax incentives, and extend patent protections.

Beyond these practical considerations has always been the strong societal impulse to prioritize treatment for conditions that are severe, are often inherited, and disproportionately affect the very young, a health care application of the “rule of rescue” [5,6]. Whether and how much the rule of rescue should drive policy-making regarding pricing and access to orphan drugs is a topic of
ongoing debate among ethicists because concepts of disease severity, young age, and genetic predisposition are not unique to rare diseases, and reimbursement decisions should in theory be made without recognition of the identity of affected individuals [7–9].

For many years, the market for orphan drugs has reflected a sort of unwritten agreement that small patient numbers could allow public and private insurers to maintain reasonable access to orphan drugs despite much higher prices. With a limited number of orphan drugs, this approach allowed innovation to be given suitable rewards, patients could receive rapid insurance coverage, and insurers could absorb high per-patient costs without experiencing destabilizing impacts to their overall budgets. However, the orphan drug landscape is shifting rapidly, with great promise for patients, but also with a growing sense of peril for health care budgets. As illustrated earlier, orphan drugs no longer are a small minority of drug approvals. The number of new regulatory submissions for orphan indications is at an all-time high; Food and Drug Administration (FDA) orphan designations totaled 350 in 2015 [8], and 41% of the drugs the agency approved in 2016 carried an orphan designation [10]. With increasing numbers of orphan drugs coming into the health system at high orphan prices, and with some drugs moving from initial orphan status to command much broader indications and “blockbuster” revenues, US decision makers have significant challenges but also an opportunity—to create an explicit framework for evaluating and pricing orphan drugs that is informed both by experiences in other countries and US-specific ethical and contextual considerations.

The Ethical Context of Funding Decisions for Treatments of Rare Diseases

There are many reasons why pricing and coverage decisions for rare diseases involve considerations that differ from those of more prevalent conditions. Many of these considerations stem from practical challenges with evidence development and with recouping development costs, given the small size of these populations. On a per-patient basis, the high research and development costs and possibility of a low return on investment make rare-disease treatments a less attractive commercial target, in principle, than interventions for more prevalent conditions [11]. This is particularly true for “ultra-rare” conditions, a term that has no formal definition, but with reported prevalence ranging from 1 per 50,000 to 1 per million population [4]. The high prices that have been set for orphan drugs are in part an outgrowth of the desire to extract a profit from a small patient base, but these higher prices have meant that these orphan drugs often do not meet commonly cited cost-effectiveness thresholds for medical interventions [12].

The fact that treatments for rare and ultra-rare conditions often fail to meet cost-effectiveness thresholds that are used to consider what a reasonable value would be for other treatments raises important ethical questions of fairness. Some ethicists and health economists have argued that fairness requires using the same standards to judge the value of treatments for all individuals [5]. In this view, the primary goal of health insurance and the health system is to use available resources to maximize the health of the population, and if resources are spent systematically for patients with rare diseases in a way that produces less health gain than could have been obtained by using the same resources to help other patients even more, this represents an unfair opportunity cost. Therefore, spending for orphan treatments that exceed the cost-effectiveness threshold applied to other treatments means that, ultimately, other “invisible” patients will be harmed.

Nevertheless, as mentioned earlier, many countries have carved out decisions regarding orphan, and particularly ultra-orphan, treatments from usual considerations of cost effectiveness. From an ethical perspective, this has been justified in several ways. First, some have argued that the goal of a health system, or of a society more broadly, is not simply to maximize health gains across the entire population. In this view, fairness can be defined as ensuring that all patients get some chance at a meaningful health gain (e.g., surviving a universally fatal childhood disease), even if this exceeds standards for what would be considered a cost-effective use of health resources [13]. This perspective on fairness is sometimes accompanied by arguments that prioritization of resources should embody the value of “fair innings”—the notion that, all things being equal, preference for curative therapy should be given to younger individuals whose circumstances have denied them the ability to live a full life, over older individuals [14,15].

There are, therefore, competing ethical interpretations of “fairness” in the context of spending on expensive treatments for rare and ultra-rare conditions. This ethical tension is captured well by Hughes et al [5]:

A key issue around whether … funding should support the provision of ultra-orphan drugs is whether the rarity and gravity of the condition represents a rational basis for applying a different value to health gain obtained by people with that condition. That ultra-orphan drugs are reimbursed at all, illustrates the fact that budget impact, clinical effectiveness and/or equity issues are given precedence over cost-effectiveness in decisions on resource allocation in some countries. The consequence, however, is that the opportunity cost of supporting the use of ultra-orphan drugs necessitates that patients with a more common disease, for which a cost-effective treatment is available, are denied treatment.

There is no simple solution to this tension; many, but not all, ethicists argue that some preference, some premium, is due to treatments for very rare conditions. But no ethicist or manufacturer, clinician, insurer, or citizen would argue that treatments for rare conditions should command an unlimited premium. To decide how much preference, how high the price for a treatment should go, is a question whose answer requires us to find an elusive balance between two different views of fairness.

Rare Disease Landscape in Health Technology Assessment and Payer Systems

For private payers in the United States, the increase in orphan drug approvals, often depending on small, noncomparative studies and surrogate endpoints, coupled with rising prices and frequent expansion beyond orphan indications, has created an atmosphere of deep concern. A recent survey of leaders at seven private insurers that comprise 75% of the US market found that more than two-thirds were concerned and monitoring the current orphan drug pipeline [16]. Despite this concern, most respondents reported that their strategic plans to manage orphan drugs are either in the earliest stages of development (initial dialogue with providers and facilities) or that they are unsure of what to do. Most payers reported the use of prior authorization requirements that are tied to FDA labeling, but relatively few described other utilization management efforts, such as requirements for genetic/diagnostic testing or ongoing monitoring for clinical improvement [16].

As the largest single insurer of children in the United States, Medicaid has a particularly important role in coverage and reimbursement for many orphan drugs, especially those that treat ultra-rare conditions. Among the 50 most costly drugs to
state Medicaid programs, 11 (22%) had orphan drug status at some point [17]. Financial pressures associated with orphan drugs have led some states to adopt prior authorization policies that have been legally challenged as inconsistent with laws that require Medicaid to not deny access to any medically necessary drug whose manufacturer participates in the Medicaid drug rebate program [18]. For example, Arkansas Medicaid instituted prior authorization criteria for a new orphan drug for cystic fibrosis, requiring patients to have first demonstrated insufficient benefit from older, less expensive therapies [19]; the state reached a legal settlement to ensure access to patients with a demonstrated need for the drug. Similarly, Pennsylvania Medicaid added severity requirements for coverage of a prophylactic treatment for hereditary angioedema that were not in the FDA label or clinical guidelines [20].

In contrast, many health technology assessment (HTA) agencies in other countries, working in partnership with public payers, have developed frameworks for decision making, thresholds for economic impact, and reimbursement policies for orphan drugs. These can be broadly lumped into the following two categories: 1) adjustments to traditional assessment of cost effectiveness and 2) development of novel approaches that do not explicitly consider cost effectiveness. Although the remit of these formalized systems is not always clear, many approaches are focused specifically on drugs to treat ultra-rare conditions. Table 1 illustrates the rare-disease considerations used by selected agencies worldwide.

<table>
<thead>
<tr>
<th>Country</th>
<th>C-E Threshold</th>
<th>BI threshold</th>
<th>Contextual factors</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>England/Wales</td>
<td>£100,000/QALY</td>
<td>£20 m per year</td>
<td>* Patient/career/family impact</td>
<td>* Allows for QALY “weighting” when QALY gain exceeds 10 years</td>
</tr>
<tr>
<td>Sweden</td>
<td>None stated (€35,000-€100,000/QALY in recent experience)</td>
<td>None stated</td>
<td>* Human dignity principle</td>
<td>* Greater degree of clinical uncertainty accepted</td>
</tr>
<tr>
<td>Netherlands</td>
<td>None stated (€80,000/QALY under discussion)</td>
<td>None stated</td>
<td>* Needs-solidarity principle</td>
<td></td>
</tr>
<tr>
<td>Canada (Ontario)</td>
<td>None</td>
<td>None stated</td>
<td>* Plausibility of treatment effects</td>
<td>* Long-term clinical modeling</td>
</tr>
<tr>
<td>France</td>
<td>None</td>
<td>€30 m per year</td>
<td>* Feasibility of randomized study</td>
<td>* Budget impact assessment</td>
</tr>
<tr>
<td>Germany</td>
<td>None</td>
<td>€50 m per year</td>
<td>* Life-threatening</td>
<td>* Clinical “stopping rules”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* No treatment alternatives</td>
<td></td>
</tr>
</tbody>
</table>

HTA, health technology assessment; C-E, cost effectiveness; BI, budget impact; QALY, quality-adjusted life-year.

In late 2016, NICE also proposed a cost-effectiveness threshold for HST technologies of £100,000 (approximately $125,000) per quality-adjusted life-year (QALY) gained, which is 3 to 5 times higher than the range of £20,000 to £30,000 used for guidance on whether non-HST technologies should be adopted [21]. After public comment, NICE revised their approach to add a QALY-weighting scheme. Specifically, if the QALYs gained for an HST technology relative to a comparator treatment over a lifetime are 30 or more, those QALYs are weighted by a factor of three. QALY gains between 11 and 29 years would receive a weight between 1.1 and 2.9, and gains of 10 or less would receive no additional weighting. Importantly, the organization notes that the potential cost to the National Health Service must also be considered before NICE can issue a positive recommendation; both HST and non-HST technologies would be subjected to a new annual budget impact threshold of £20 million. In cases in which the threshold is exceeded, the manufacturer is expected to propose methods of managing the budget impact to the National Health Service [21]. Other countries acknowledge that cost-effectiveness considerations should be relaxed for orphan drugs but do not provide alternative thresholds to consider. Sweden, for example, considers the following three principles when making value

determinations on drugs: a human dignity principle, which dictates that all citizens should be treated equally despite personal characteristics or societal status; a needs-solidarity principle, which prescribes that the health system should provide equal access to care for all and strive for optimized clinical benefit based on patient need; and a cost-effectiveness principle, indicating that the health system should strive for balance between costs and effects [22]. The higher the level of need as assessed using the first two principles, the more relaxed the threshold for determining cost effectiveness, although there are no specific parameters provided on what that threshold should be. In practice, most of the Swedish HTA decisions for orphan drugs involve cost-effectiveness estimates that range between €35,000 and €100,000 per QALY gained, depending on the severity of the condition [23]. However, the agency has denied coverage for orphan drugs, as in the case of Cerezyme® (Genzyme Corporation, Cambridge, MA) for Gaucher disease, for which the estimated cost effectiveness of €1 million per QALY was determined to be too high a price to pay for any level of benefit [24].

Value determinations for orphan drugs in certain other jurisdictions do not include assessments of cost effectiveness at all. In Canada, a rare disease evaluation framework has been developed and implemented for several decisions made by the Ontario Public Drug Programs [12,25]. The framework has seven steps, as outlined in Fig. 1. Suitability for the framework is determined based on 1) adequate evidence from clinical studies, including determination of whether traditional randomized trials are feasible given condition rarity, and 2) a threshold for rarity, defined in this case as an incidence (births or new diagnoses) of 1 in 150,000 per year. The next steps involve reviewing the natural history of disease and potential effectiveness of treatment, using available clinical data and a set of criteria to assess the biologic plausibility, temporal relationship, dose-response, consistency, and other elements of drug effect [26]. Long-term effectiveness is then integrated into a disease model to explore uncertainty, and costs are evaluated as part of a budget impact model.

In practice, recommendations to fund each of the orphan drugs approved under this framework have been paired with ‘stopping rules’ that have been agreed on in consultation with clinical experts, with reimbursement discontinued for patients who do not continue to show clinical improvement. For example, continued reimbursement for idursulfase (Elaprase®; Shire Human Genetic Therapies, Inc., Lexington, MA) for Hunter’s syndrome is contingent on 1) no or minimal progression of neurocognitive impairment, 2) absence of need for chronic invasive mechanical ventilation, and 3) ability of the patient to ambulate [27].

**Beyond Cost Effectiveness: The Role of Contextual Factors in Rare Diseases**

There are methodologic challenges to conducting economic evaluations in rare diseases and several proposals for how to address these challenges; such information is beyond the scope of this review. Nevertheless, some health economists argue that there are always value considerations that go beyond costs and QALYs when evaluating any health care intervention, whether for a rare condition or not, and that some countries explicitly consider other criteria when assessing treatments for rare diseases [28]. It is possible that a full and proper weighing of these other benefits or disadvantages, and full consideration of relevant contextual considerations, when combined with traditional cost-effectiveness results, would lead to an appropriate valuation of treatments for rare and common conditions [29].

Some stakeholders have expressed concern that qualitative consideration of these external factors will always receive less emphasis when quantitative evaluations (such as cost-effectiveness ratios) are also available. To help ensure that nonquantified benefits, disadvantages, and contextual considerations are given appropriate attention alongside clinical and cost-effectiveness data, there have been proposals to formalize the enumeration and evaluation of such factors [30,31].

One set of proposals involves developing a formal framework for the structured evaluation of specific domains that may be relevant to assessing the value of health care interventions. Such a framework would explicitly list the domains and aspects of value that should be captured in any assessment [31,32]. When valid, quantifiable results are available for specific domains, these would normally be included in standard clinical and cost-effectiveness analyses. However, when such results are not available, this could be noted, and a description of the available evidence (whether quantitative or qualitative) could be included for each domain.

To avoid double counting, the domains to be considered would need to be comprehensive and mutually exclusive, to the extent possible. To ensure that all relevant domains are considered, frameworks would need to be developed with the input of all relevant stakeholders, including patients with the conditions under consideration. For example, such a framework might consider economic efficiency to be sufficiently covered by existing economic analyses but perceive a need to explicitly include a domain for access to health care interventions. Other domains often mentioned as being excluded from traditional evaluations include the value of hope and the value of innovation, per se [33]. Still other domains might include one or more of the ethical considerations previously listed as especially relevant for rare diseases, such as unmet need, disproportionate effects on the very young, lack of alternative treatments, the “rule of rescue,” or other equity/access issues [29].

Beyond identification of the relevant domains to consider alongside clinical and cost effectiveness, there is the question of how to combine and weigh the impacts of specific interventions on these domains. This may be conducted informally and ad hoc, with decision makers subjectively weighing these impacts internally before arriving at a judgment. As Nicod et al. have pointed out: ‘The main criticisms of this process is the lack of accountability for reasonableness’ given that there is not always a clear process to account for the inclusion of these forms...
of evidence in the assessment process, as well as the lack of consistency in accounting for these ‘other considerations’” [33]. At the other end of the analytic spectrum, multi-criteria decision analysis may be utilized, in which the values assigned to each domain and the weights used to combine them are determined through a formal process and made explicit and public [31,34,35]. If more than one decision maker is involved, thought must also be given to how to combine the valuations of individuals to arrive at a common decision (e.g., majority vote or consensus). Choosing between these approaches may involve value judgments and have impact on the evaluation of treatments for rare conditions. Walker has pointed out that formal multi-criteria decision analysis is relatively transparent and rigorous but also requires additional resources and has the risk of “channeling debate” via the scoring/weighting decisions that are taken [34]. To ensure transparency and procedural fairness, enough detail would need to be provided on both the process and the deliberations that are part of such decisions, including how quantitative and qualitative inputs were combined and weighted [28].

Summary: The Way Forward

As alluded to by the title of this article, there is simply no magic solution to the conundrum of assessing the evidence on clinical effectiveness, economic impact, and value of drugs to treat rare diseases. Assessors of evidence must determine whether different standards should be used to determine the net health benefit of a rare-disease intervention; decision makers must decide whether and how to allow contextual factors to accompany more traditional methods of evidence synthesis and economic evaluation; and above all, societies must choose how far they are willing to go to tip the scales toward equity and away from equality. In other words, how much health for other individuals are we willing to give up to make a special case for rare-disease drugs?

The regulatory community worldwide has already put into place measures to accommodate orphan drugs. Both the FDA and European Medicines Agency have stated thresholds for what constitutes a rare disease, are legislatively empowered to provide incentives for manufacturers to develop drugs for rare diseases, and have a variety of accelerated approval pathways targeted at these agents [36–38]. And, as we describe, many HTA agencies and public payers worldwide have developed and operationalized their own specific approaches for accommodating orphan drugs.

Although the merits and pitfalls of the different approaches described here can be debated, what is clear is that neither the public nor private payer community in the United States has fully engaged in the discussion. This is in part because there is no central agency tasked with determining whether rare diseases deserve special status in terms of evaluation, valuation, and pricing, but that is not the only reason. As we have highlighted in this article, even though the international community has taken steps to address these issues, most recently with the publication of a core set of principles from a multi-stakeholder European working group [39], it has done so with a high degree of variation. The way forward will therefore require a coalescing of approaches internationally to define the level of rarity requiring special action, to determine what adaptations of traditional HTA are required, the types of special pricing and access considerations that are necessary, and willingness among major US decision makers to fully embrace these approaches.

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