Assessing the Effectiveness and Value of Drugs for Rare Conditions

A Technical Brief for the ICER Orphan Drug Assessment & Pricing Summit

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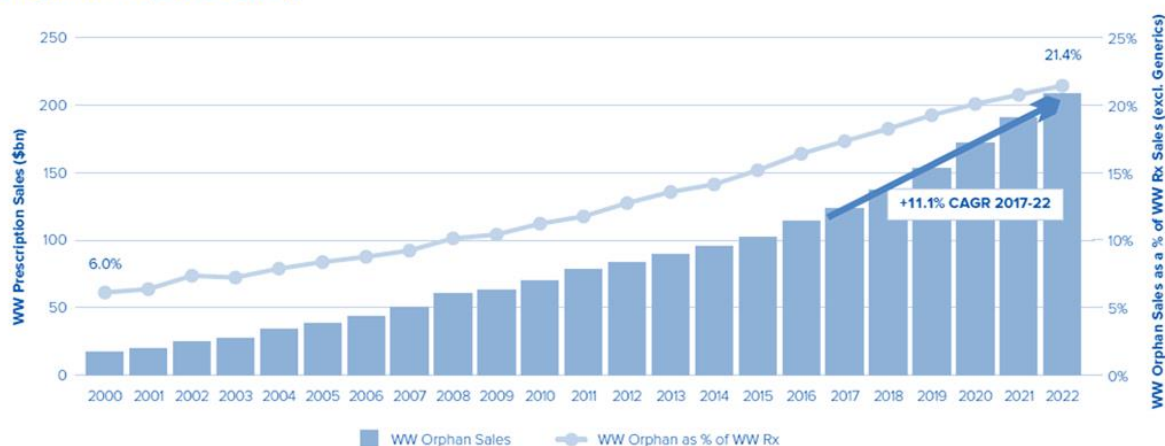*Steven D. Pearson, MD, MSc, President, ICER*

Introduction

The National Organization for Rare Diseases (NORD) estimates that approximately 30 million Americans are affected by one of 7,000 rare diseases.[1] Biopharmaceutical products targeted at these rare conditions are often called "orphan drugs." In recent years, approvals 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. As shown in Figure 1 below, 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.

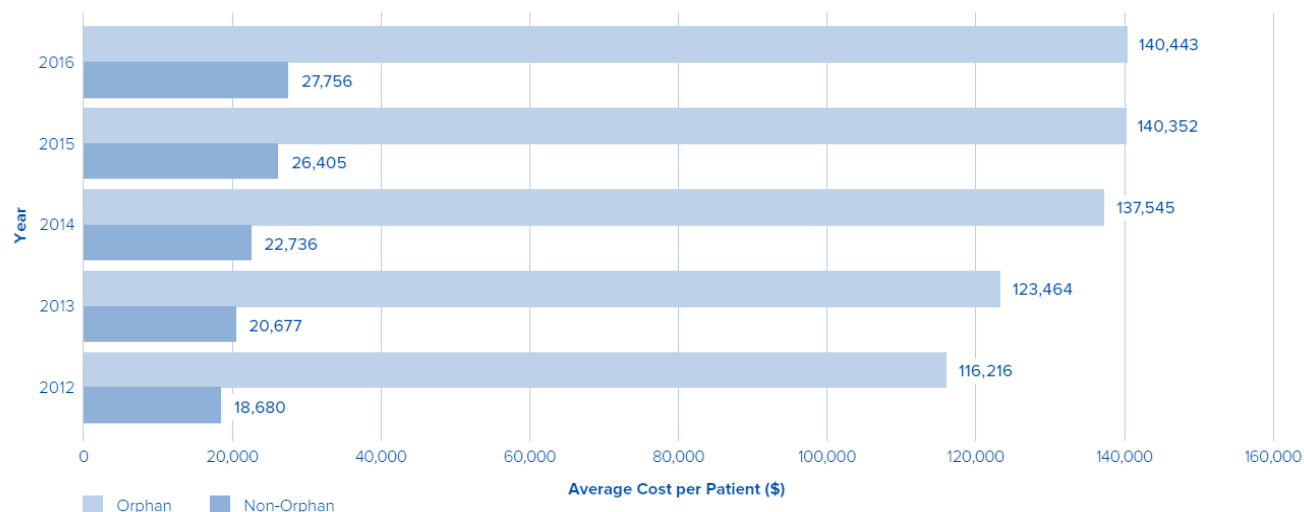**Figure 1. Orphan drug sales and market share trends.**

CAGR: Compound Annual Growth Rate

One factor driving orphan drug costs has been an increase in the price for orphan drugs. As shown in Figure 2, when considering publicly available prices before insurer rebates or discounts, the average annual costs of orphan drugs are five times higher than those of non-orphan medications.

Figure 2. Average annual costs of orphan and non-orphan drugs.

Average Cost per Patient per Year 2012-2016

Historically, higher prices for orphan drugs have not been associated with greater barriers to insurance coverage, 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 was a general sense that what can be termed "orphan prices" needed to be high on a per-patient basis in order for innovators to make a reasonable profit after recouping research and development costs. Beyond these practical considerations has always been the strong societal impulse to prioritize treatment for conditions that are severe, inherited, and disproportionately affect the very young. This impulse is strong, reflecting what ethicists have called the "rule of rescue."[3,4] Whether and how much the rule of rescue should drive policymaking regarding pricing and access to orphan drugs is a topic of ongoing debate among ethicists.[4,5]

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. Innovation was given suitable rewards, patients received rapid insurance coverage, and insurers were able to absorb high per-patient costs without seeing 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 are no longer 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,[6] and 41% of the drugs the agency approved in 2016 carried an orphan designation.[7] 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, concerns are growing that new

policy solutions will be needed to maintain the difficult balance between incentives for innovation, patient access, and affordability to patients and society.

In this technical brief, we seek to describe further the distinctive clinical, regulatory, and payer landscape for treatments of rare and ultra-rare conditions in the US. We will also summarize the ethical and operational challenges in conducting value assessments of orphan and ultra-orphan drugs. These challenges will be crystallized in a case study of nusinersen (Spinraza®, Biogen Idec), the first available biopharmaceutical for spinal muscular atrophy (SMA). Available data and assessment challenges identified in this case will be contrasted with other recent examples. The purpose of the entire brief is to inform further discussion of the methods that ICER and other assessment groups should use to assess the effectiveness and value of orphan treatments and to suggest associated methods for establishing a value-based price range for these drugs.

Background

Definitions

One of the key challenges in policy discussions focused on treatments for rare diseases is in settling on a working definition of what constitutes a "rare" or "ultra-rare" condition. Note that, while the presentation of these definitions differs in practice, we present them in terms of prevalence thresholds per 100,000 population to enable comparisons across definitions. A recent survey of definitions from over 1,100 organizations worldwide found significant variation, ranging from prevalence thresholds of five to 76 cases per 100,000 population.[8] In this analysis, patient organizations tended to have the most liberal definitions (average: 46 per 100,000; maximum: 150), while private payers had the most restrictive (average: 28 per 100,000; maximum: 64).

Some countries have made rare disease definitions a component of laws establishing distinctive patent, tax, and regulatory provisions that provide enhanced incentives for orphan drug development. In the United States, the Orphan Drug Act of 1983 established a definition for use by the Food & Drug Administration (FDA) based on a prevalence of <200,000 patients, which today, given a current estimate of US population size of 326 million, would represent approximately 61 cases per 100,000. The European Union's definition, which affects joint public health actions and regulatory submissions to the European Medicines Agency (EMA), is somewhat lower (50 per 100,000).[9] Finally, Japan considers diseases to be rare if they affect fewer than 50,000 patients, or <40 per 100,000 given current population estimates.

Neither in the US nor in other countries is there an explicit definition used by regulatory processes to identify a boundary between rare and "ultra-rare" conditions, but many countries have established separate procedures for consideration of funding treatments for patient populations that are much smaller than the lower bounds of the standard orphan population size.[10] For example, the health technology assessment (HTA) agency in Italy considers a disease prevalence of one per million to represent an ultra-rare disease, while the National Institute for Health and Care Excellence (NICE) in England restricts entry into a separate assessment track named the Highly Specialized Technologies (HST) program to diseases with a prevalence of two per 100,000 or less.[8,11]

Definitional boundaries for rare and ultra-rare disease have become more complicated and controversial because of the application of the term to subsets of more prevalent conditions. Orphan regulatory pathways are increasingly being used for treatments targeted at specific biomarkers or genetic mutations, such as ALK mutations in non-small cell lung cancer, in which a genetically defined subpopulation of fewer than 200,000 individuals is nested within a much larger overall disease cohort. A recent analysis of FDA approvals from 2009-2015 found that over one-quarter of orphan drug approvals in oncology were for such biomarker-defined subsets.[6] This has

raised questions regarding whether the intent of Congress in establishing the Orphan Drug Act, and the incentives imagined necessary at that time to spur innovation for orphan drugs, are still a good match for a changed environment witnessing a thriving market for treatments of genetically defined disease subsets (see page 6 for further discussion).

The Ethical Context of Funding Decisions for Treatments of Rare Diseases

There are a number of reasons why pricing and coverage decisions for rare diseases involve considerations that differ from those of more prevalent conditions. As mentioned previously, many of these considerations stem simply from 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.[12] The high prices that have been set for orphan drugs are in part an outgrowth of the perceived need to achieve "reasonable" profit from a small patient base, but these higher prices have meant that these orphan drugs rarely meet commonly accepted cost-effectiveness thresholds that represent the foundation of judgments of value for other drugs.[13]

The fact that treatments for orphan and ultra-orphan conditions often "fail" to meet cost-effectiveness thresholds 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. 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 exceeds the cost-effectiveness threshold applied to other treatments means that, ultimately, other "invisible" patients will be harmed.[3]

However, as mentioned earlier, there is a long history across many countries of carving out decisions regarding orphan, and particularly ultra-orphan treatments, from the usual considerations of cost-effectiveness that are applied to pricing and coverage for other parts of the health system. 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, even if this leads to spending that produces less overall health gain across the entire population.[14] 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 should be given to younger individuals whose circumstances

have denied them the ability to live a full life – these patients, unlike the elderly who fall ill late in life, have not had their fair share of innings.[15,16]

In addition to these arguments, many rare diseases have specific characteristics that may merit additional consideration: they are often severe, frequently leading to rapid death or significant disability; many are manifest in infants and young children; and they have often have no effective treatment options other than supportive care. Conditions with these characteristics not only have a significant impact on the lives of patients, but on their families and caregivers as well, who often must abandon their roles at home or work to care for their loved one and be the primary point of contact for insurers and disability programs, all of which generates significant stress and anxiety. As an example, a recent multi-country study estimated the annual costs of caring for a 12-year-old boy with Duchenne muscular dystrophy to exceed $120,000, of which less than half were direct medical costs.[17]

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 and colleagues:

> *"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."[3]*

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, or clinician, or 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 Regulatory and Payer Systems

As mentioned above, the FDA considers a disease to be rare if it affects fewer than 200,000 individuals; that threshold is used to create an orphan drug designation in the regulatory pathway. This designation derives from the Orphan Drug Act of 1983, which was intended to provide a series of financial incentives and accelerated approval pathways to encourage increased development of drugs for rare and severe conditions.[18] Incentives within the Orphan Drug Act include:

- 7 years of market exclusivity for the approved indication(s)
- 50% tax credit on research and development costs
- Access to a pool of research grants to fund Phase I-III clinical trials
- User fees waived for regulatory submissions

Orphan drug submissions are also frequently granted faster routes to regulatory approval through either "priority review" (review cycle of six months vs. the standard 10 months) and/or "accelerated approval" (approval based on surrogate endpoints the agency feels are reasonably likely to predict clinical benefit). Incentives and benefits for orphan drugs are also available in the EU, and include a mix of market exclusivity, protocol and administrative assistance, reduced fees, and additional incentives for small-to-medium sized companies.[9]

One effect of these modified pathways is on the type and amount of evidence on clinical effectiveness available at the time of FDA approval. A recent analysis of trial characteristics in orphan and non-orphan cancer drug submissions indicated that pivotal orphan drug trials had significantly fewer randomized multi-arm designs (30% vs. 80% for non-orphan trials, p=.007), significantly more open-label designs (91% vs. 67%, p=.04), and a primary endpoint of disease response rather than disease progression or survival (68% vs. 27%, p=.04).[19]
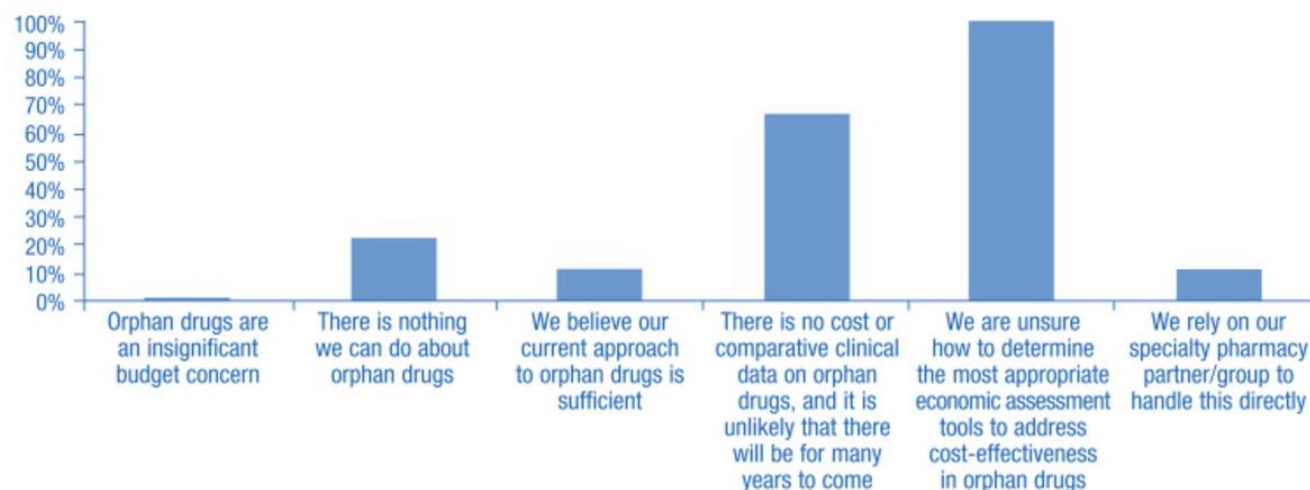
There has been debate recently over whether some manufacturers have sought to gain a first FDA approval for an orphan condition in order to benefit from the incentives in the Orphan Drug Act, with an ultimate goal of acquiring additional indications as rapidly as possible thereafter in order to increase the patient populations using the drug. Analyses have shown that many orphan drug submissions for treatment of biomarker-defined patient subgroups have resulted in the addition of new indications and/or significant off-label uses after approval.[6] Concerns have therefore been raised that some manufacturers are "gaming" the system, receiving incentives, tax credits, and accelerated regulatory time horizons for what are ultimately non-orphan drugs. In March of 2017, US Senators Tom Cotton, Charles Grassley, and Orrin Hatch submitted a letter to the Government Accountability Office requesting an investigation into possible abuses of the Orphan Drug Act; an investigation is ongoing.[20]

For private payers in the US, the increase in orphan drug approvals, often contingent on less-than-robust evidence, and 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 over two-thirds were concerned and monitoring the current orphan drug pipeline.[21] 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. Nearly all private payers reported that they have not yet determined the most appropriate methods for assessing the potential economic impact of orphan drugs (see Figure 3).

Figure 3. Actions taken for orphan drugs.

Q: If you have no plans in place, what actions are you taking?

Source: Handfield R, Felstein J. Insurance companies' perspectives on the orphan drug pipeline. American Health and Drug Benefits 2013;6(9):589-98.

As the largest single insurer of children in the US, 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.[22] Financial pressures associated with orphan drugs has led some states to adopt prior authorization policies that have been legally challenged as being inconsistent with laws requiring Medicaid not deny access to any medically necessary drug whose manufacturer participates in the Medicaid drug rebate program.[23] For example, Arkansas Medicaid instituted prior authorization criteria for a new orphan drug for cystic fibrosis that required patients to have first demonstrated insufficient benefit from older, less expensive therapies;[24] 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.[25]

Internationally, many HTA agencies 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 two categories: (a) adjustments to traditional assessment of cost-effectiveness; and (b) development of novel approaches that do not explicitly consider cost-effectiveness. While 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 1. Formalized approaches to assessment and consideration of clinical and economic evidence by selected HTA agencies worldwide.

Country	C-E Threshold	BI Threshold	Contextual Factors	Other Considerations
England/Wales	£100,000/QALY	£20m per year	• Patient/carer/family impact • Benefits other than health/social • Impact on care delivery/training	• Allows for QALY "weighting" when QALY gain exceeds 10 years
Sweden	None stated (€35,000-€100,000/QALY in recent experience)	None stated	• Human dignity principle • Needs-solidarity principle • Cost-effectiveness principle	• Higher degree of clinical uncertainty accepted
Netherlands	None stated (€80,000/QALY under discussion	None stated	None stated	• Medical necessity • Clinical effectiveness • Disease burden • Feasibility (budget impact)
Canada (Ontario)	None	None stated	• Plausibility of treatment effects • Feasibility of randomized study	• Long-term clinical modeling • Budget impact assessment • Clinical "stopping rules"
France	None	€30m per year	• Life-threatening • No treatment alternatives	None stated
Germany	None	€50m per year	None stated	• Lower levels of statistical significance • Surrogate endpoints acceptable

C-E: Cost-effectiveness; BI: Budget impact; QALY: Quality-adjusted life year

Perhaps the most prominent and recent example of an adjustment to formal cost-effectiveness analysis is the approach proposed by the National Institute for Health and Clinical Excellence (NICE) in the UK. This approach applies to therapies evaluated in NICE's Highly Specialized Technologies (HST) program, defined as interventions for populations with a prevalence of two per 100,000

population or less (approximately 1,300 individuals in the UK). The HST program has been in place since 2013. While the process and logistics are similar to those of a single technology assessment for a non-orphan drug, the framework for evaluation in the HST program is broader, with domains and criteria as listed below:

- Nature of the condition, including impact on patients and caregivers
- Impact of the new technology, including health benefits and robustness of evidence
- Budget impact, both broadly and specifically on the budget for specialized services
- Impact of the new technology beyond health benefits, including elements outside the National Health Service and personal social services
- Impact of the new technology on the delivery of specialized services, including staff training needs

In late 2016, NICE also proposed a cost-effectiveness threshold for HST technologies of £100,000 (approximately $125,000) per QALY gained, which is three to five times higher than the range of £20,000-30,000 used for guidance on whether non-HST technologies should be adopted.[11] Following public comment, NICE revised their approach to add in a QALY-weighting scheme. Specifically, if the QALYs gained for an HST technology relative to a comparator treatment over a lifetime are 30 or higher, those QALYs are weighted by a factor of three. So, for example, if an orphan drug is estimated to add £10 million in cost over a lifetime and provide 40 years of quality-adjusted survival, the unweighted cost-effectiveness ratio would be £250,000 per QALY gained, exceeding the HST threshold. With the weight of three applied, the ratio would be £83,000 per QALY gained, which would fall beneath the threshold. 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 where the threshold is exceeded, the manufacturer is expected to propose methods of managing the budget impact to the NHS.[11]
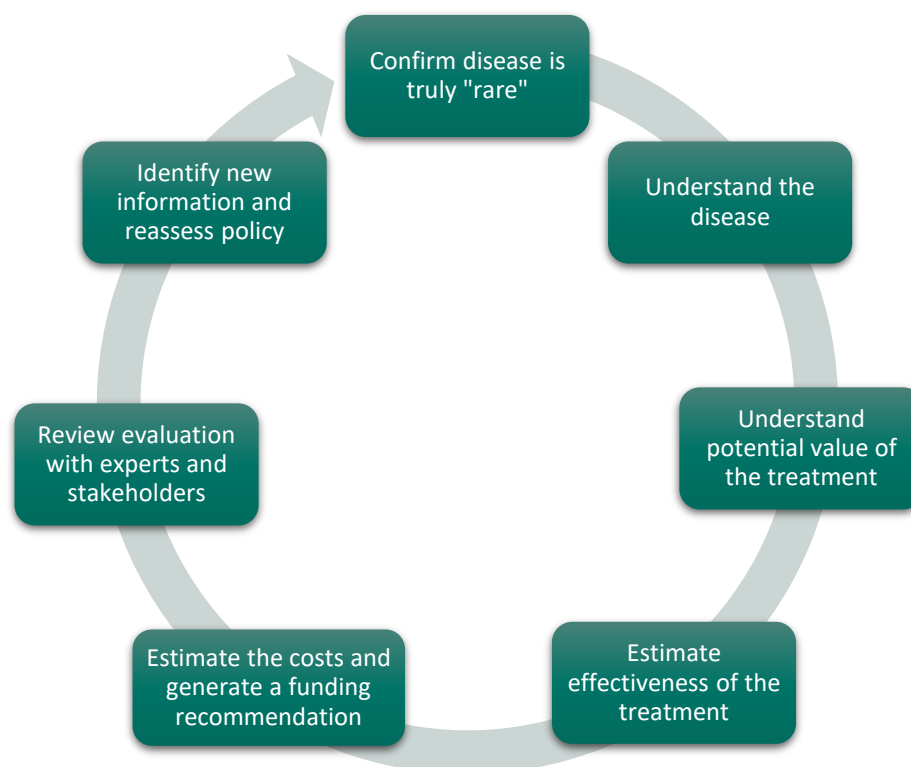
Other countries acknowledge that cost-effectiveness considerations should be relaxed for orphan drugs, but do not provide alternative thresholds to consider. Sweden, for example, considers three principles when making value determinations on drugs: a human dignity principle, which dictates the all citizens should be treated equally despite personal characteristics or standing in society; 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.[26] 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 - €100,000 per QALY gained, depending on the severity of the condition.[27] However, the agency has denied coverage for orphan drugs, as in the case of Cerezyme® for Gaucher disease; the estimated cost-effectiveness of €1 million per QALY was determined to be too high a price to pay for any level of benefit.[28]

Similarly, the Netherlands considers cost-effectiveness findings alongside assessments of medical necessity, clinical effectiveness, and feasibility (primarily examined as a function of potential budgetary impact).[29] The country's HTA agency does not use a single threshold, but allows for tailored consideration, with conditions carrying the greatest disease burden allowed the most leeway. That said, the agency is currently arguing for a maximum threshold of €80,000 (about $85,000) per QALY, although higher levels might be considered acceptable in certain situations.

Other jurisdictions have abandoned any notion of using cost-effectiveness in value determinations for orphan drugs. In Canada, a rare disease evaluation framework has been developed and implemented for several decisions made by the Ontario Public Drug Programs.[13,30] The framework has seven steps, as outlined in Figure 4 below.

Figure 4. Ontario policy framework for funding rare-disease interventions.

Adapted from Winquist E, et al. An evaluation framework for funding drugs for rare diseases. Value in Health 2012;15:982-6.

Suitability for the framework is determined based on (a) adequate evidence from clinical studies, including determination of whether traditional randomized trials are feasible given condition rarity; and (b) a threshold for rarity, defined in this case as an *incidence* (births or new diagnoses) of one in 150,000 per year. The next steps involve reviewing the natural history of disease and potential effectiveness of treatment, using available clinical data as well as a set of criteria to assess the biologic plausibility, temporal relationship, dose-response, consistency, and other elements of drug effect.[31] 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 upon 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) for Hunter's Syndrome is contingent on (a) no or minimal progression of neurocognitive impairment; (b) absence of need for chronic invasive mechanical ventilation; and (c) ability of the patient to ambulate.[32]
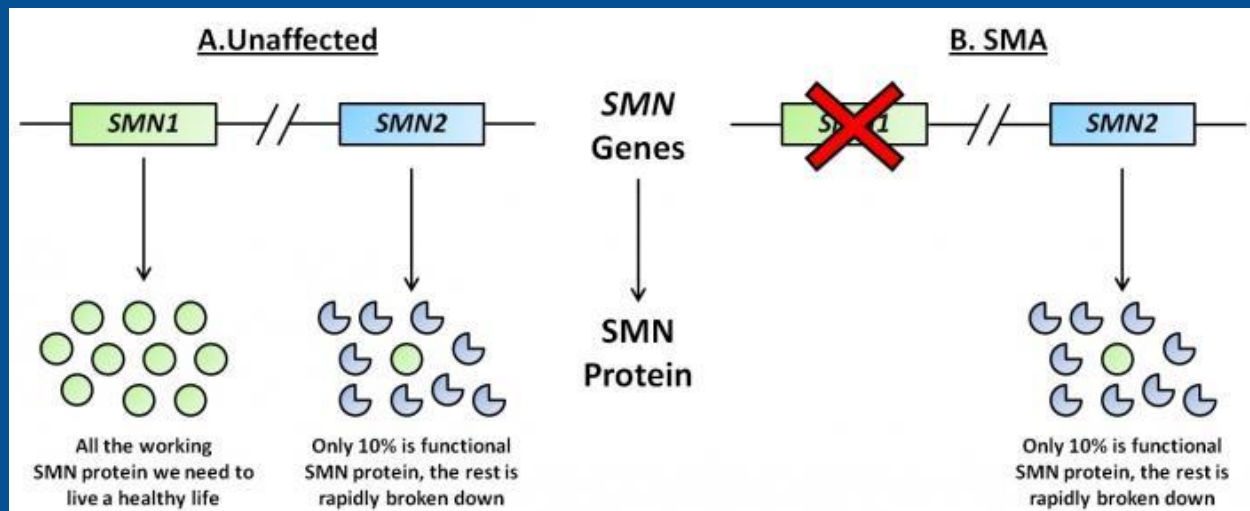
Other jurisdictions have made adjustments primarily to clinical review processes for orphan drugs, with budget impact as the sole economic factor of interest. In fact, the pan-Canadian Pharmaceutical Alliance, which negotiates reimbursement arrangements with manufacturers on behalf of all provinces and territories, recently ended negotiations with Alexion over the funding of eculizumab (Soliris®) for atypical hemolytic uremic syndrome based on the drug's high cost alone.[33] France also allows temporary authorization to be triggered for any rare condition considered to be imminently life-threatening, and allows for a fast-tracked review for drugs addressing high unmet need and with demonstrated efficacy and tolerability. If these conditions are met, then any therapy with an annual budget impact under €30 million is considered proven and therefore reimbursed.[27] Germany, which does not assess cost-effectiveness for any drug, orphan or non-orphan, allows for more liberal thresholds for statistical significance (e.g., $p < 0.10$ vs. traditional 0.05) in its evaluation of clinical effectiveness for orphan drugs, accepts evidence on surrogate endpoints alone, and any clinical benefit identified is considered proven if budget impact does not exceed €50 million per year.[27]

Case Study: Spinraza

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive disorder that affects approximately one in 11,000 live births.[34] SMA is caused by mutation and/or deletion of the survival motor neuron 1 (*SMN1)* gene, a gene that is critical for the maintenance of motor neurons. A nearly identical, but less functional, gene (*SMN2*) serves as a backup, and severity of SMA is generally considered to be inversely correlated with the number of *SMN2* copies present (Finkel 2015) (see Figure 5 below). The disease is characterized by five major clinically-defined subtypes. Type 0 SMA manifests at birth and patients rarely survive past six months. Type 1 is the most common, affecting approximately 60% of patients. It is diagnosed in infancy; babies with SMA Type 1 never sit, roll, or walk, require invasive ventilation, and typically die by age 2.[35] Children with Type 2 are diagnosed between seven and 18 months, can sit (but not stand) independently and have a shortened lifespan. Individuals with Type 3 SMA are diagnosed after 18 months of age, have varying degrees of ambulation, and have a normal lifespan, but these patients also experience significant muscle weakness and disability. Finally, Type 4 SMA, the most uncommon type, presents in adulthood (patients in their 20s and 30s) and typically involves milder and/or transient levels of muscle weakness, with no impact on survival.[36] There are approximately 9,000 patients living with SMA in the US today; Type 1 patients comprise only 14% of this total, given the rapidly fatal nature of this form of SMA.[37]

Figure 5. Illustration of SMN1 and SMN2 genes, in (a) unaffected individuals and (b) SMA.

Source: SMA Support UK. Accessed at: http://www.smasupportuk.org.uk/blog/research/azzouz-laboratory-gene-therapy-for-sma, May 2017.

Diagnosis of SMA is made via clinical assessment and laboratory testing for the mutation or deletion of the *SMN1* gene. Testing for the number of copies of the *SMN2* gene is also available, but there is currently no consensus on how to determine whether the copies of *SMN2* are fully functional, so current clinical guidance suggests that the number of *SMN2* copies be considered a relatively loose correlate of disease severity and prognosis.[38] In addition, there are variations in severity even within SMA subtypes, which generally track with the age at which invasive respiratory support is needed.[39]

As mentioned above, patients with the most severe forms of SMA require respiratory assistance, along with nutritional support for cases with feeding difficulties. Supportive care can prolong life expectancy, but its invasive nature can exact a toll on patients and their families. A comparison of survival among SMA Type 1 patients in Italy showed improved survival for those receiving continuous invasive mechanical ventilation versus noninvasive ventilation or other respiratory muscle aid (median 76 vs. 29 months, p<.001), but also a significant decrease in the number of parents choosing invasive ventilation over the course of the study.[35] For many parents, the choice between invasive treatment and palliative care is an intensely personal one that is complicated by ethical concerns as well as the feasibility of handling the intense caregiver burden that is present.[40]

Supportive care for early-onset SMA is also quite expensive. A recent analysis of direct medical costs for neuromuscular disorders among commercially-insured patients found that SMA (Types 1, 2, and 3) generated direct medical costs that exceeded $120,000 per year, including nearly $10,000 in out-of-pocket costs;[41] estimates of indirect costs, including lost income for family caregivers, ranged from $35,000 - $108,000 annually.

There are a number of outcome scales that have been utilized in epidemiologic studies and clinical trials of Type 1 SMA, including Hammersmith Infant Neurological Exam, Part 2 (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). Other tests, such as the Hammersmith Functional Motor Scale, Expanded (HFSME), and the six minute walking test, are more applicable to later-onset forms of SMA. Importantly, while these scales have been validated statistically and are supported by clinical research groups as standard outcome measures, there is not yet a uniformly-accepted definition of a minimally-important clinical difference for any of them.[38] Patients with SMA are treated at a number of specialized clinics in the US, including several children's hospitals and other academic medical centers. Many of these are members of the NIH-funded Neuro-NEXT network, which conducts clinical trials in SMA and a variety of other neurologic conditions (www.neuronext.org).

Spinraza™ (nusinersen, Biogen Idec)

Spinraza is an antisense oligonucleotide that interacts with transcription of available copies of the *SMN2* gene, generating full length and functional SMN proteins that are absent in SMA patients due to the deletion of *SMN1*.[42]

Spinraza is delivered via intrathecal (into the spinal canal) injection. Four loading doses are followed by maintenance doses every four months. Spinraza was approved by the FDA in December 2016, and is indicated for use in all types of SMA. The list price of Spinraza is $125,000 per injection, which translates into approximately $750,000 for administration of the drug during the first year and $375,000 per year subsequently. These costs do not include other physician or facility fees associated with administration of the drug.

Currently, the only publicly-available Phase III clinical evidence for Spinraza is the ENDEAR study, a double-blind, randomized clinical trial in which 121 patients with Type 1 SMA were randomized 2:1 to receive Spinraza or sham injection;[43] patients were a median of six to eight weeks of age at symptom onset. Double-blind status was preserved for at least six months, when an interim analysis was conducted. Patients could then continue on an open-label extension for further evaluation.

The FDA's evaluation centered on the proportion of responders, identified as those with improvement in more categories (e.g., kicking, crawling, rolling) on the HINE-2 than worsening. Of the 52 Spinraza patients eligible for the interim analysis, 21 (40%) were classified as responders, versus zero in the sham control group (p<.0001). In addition, an assessment of event-free survival, based on time from treatment initiation to permanent ventilation or death, yielded substantial benefits in the Spinraza arm. A total of 49 Spinraza patients (61%) were alive and event-free as of one year, versus 13 (32%) in the control arm (Hazard

Ratio [HR]: 0.53; p=.005). Rates of adverse events among Spinraza patients were comparable to or lower than event rates in the sham arm. The open-label extension of ENDEAR, known as SHINE, continues, as does EMBRACE which includes Type 1 and 2 patients who did not meet age or other criteria for entry into other Spinraza trials.

Another Phase III sham-controlled trial, CHERISH, was conducted in patients with Type 2 or 3 SMA who were age two to 12 years and had symptom onset after six months of age; data were presented in April 2017 at the American Academy of Neurology annual meeting. Public documents are currently restricted to the company's press release and abstract submission, which state that Spinraza-treated patients had a mean 3.9-point improvement on the HFSME at 15 months, while sham patients declined an average of one point (p<.0001 for difference), and a greater number of Spinraza patients had a ≥3-point increase in HFSME score (57.3% vs. 20.5% for sham; p-value not reported).[44,45] However, another measure, the percentage of patients achieving new World Health Organization (WHO) motor milestones (e.g., from hands-and-knees crawling to walking with assistance), differed more modestly (17.1% vs. 10.5% for Spinraza and sham respectively, p-value not reported).

Finally, interim data from NUTURE, an open-label, single-arm study of 20 infants less than six weeks old with genetically-diagnosed, presymptomatic SMA, were also presented at the AAN meeting. At a median of 317.5 days of follow-up, all infants were alive, none required respiratory intervention, and most infants were achieving motor and growth

milestones consistent with normal development.[45]

Evidence Comparison: Spinraza versus Other Orphan Drugs

In order to provide context for the clinical evidence available for Spinraza at the time of approval, we examined the prescribing information for Exondys 51™ (eteplirsen, Sarepta) an orphan drug approved in September 2016 for the treatment of Duchenne muscular dystrophy (DMD), as well as information on several orphan drugs approved in earlier decades for lysosomal storage disorders (Pompe disease and Gaucher disease).[46-49]

The diseases of focus vary in terms of their natural history and the trajectory of their clinical course. For example, Myozyme® (alglucosidase alfa, Sanofi Genzyme) was approved based on data on its effects in infantile-onset Pompe disease, which has a severity of clinical course and fatality rate similar to Type 1 SMA.[50] In contrast, Exondys 51 was studied in a specific type of DMD that also is typically fatal, but over a longer clinical course.[51] Finally, Type 1 Gaucher disease, for which both Cerezyme® (imiglucerase, Sanofi Genzyme) and VPRIV®(velaglucerase, Shire) were approved, has a more heterogeneous natural history, with symptoms presenting at any point in childhood or adulthood.[52]

The evidence base for these drugs considered at the time of approval also seems to differ according to disease severity and homoegeneity. Spinraza, Exondys 51, and Myozyme were all studied in controlled RCTs, although the type of control differed (i.e.,

sham/placebo for Spinraza and Exondys 51, historical control only for Myozyme). In contrast, comparative studies of Cerezyme and VPRIV were limited to RCTs of multiple doses of active drug without other control, or non-inferiority studies involving comparisons to other enzyme replacement agents. The ENDEAR study of Spinraza (n=121) was larger than the evidence base at approval for any of the other drugs (range: 15-39 patients), which may be a function in part of Type 1 SMA's prevalence relative to the other conditions.

Outcome measurement also seemed to track closely with disease severity. Mortality and requirements for ventilation were both key endpoints in the ENDEAR trial as well as both RCTs of Myozyme, while surrogate endpoints were used in the Exondys 51 trials (dystrophin productions, six minute walk test). Studies of the Gaucher disease interventions focused only on biomarker/laboratory changes, as skeletal effects are difficult to measure and their response to treatment is slow.[53] Finally, a key consideration for any orphan drug, especially one with a novel method of action or use of experimental technology for treatment delivery (e.g., viral vectors), is durability of effect. At the time of FDA approval, patients had been followed for as little as six and as much as 20 months. The longest periods of follow-up were again for more severe conditions (Type 1 SMA and Pompe disease, 14 months and 12-20 months respectively).

Payer Reaction to Spinraza

Payer response to the Spinraza approval has been mixed. National payers Anthem and Humana currently provide coverage only for

Type 1 SMA and require monitoring every six months for improvement in symptoms and motor milestones as well as avoidance of invasive ventilation in order to continue treatment.[54,55] Aetna, on the other hand, covers Spinraza for all but Type 4 disease, without any monitoring requirements.[56] UnitedHealth's policy is a hybrid of these, allowing coverage for all but Type 4 disease, but requiring ongoing monitoring to ensure avoidance of ventilation for continuation of therapy.[57]

Spinraza: Value Assessment Challenges

As described elsewhere in this brief, there are a number of challenges in applying traditional methods of economic evaluation to orphan drug situations generally, and these certainly apply to the Spinraza case as well. For one, quality of life data is problematic to ascertain in the very young; information is often collected from caregivers acting as proxies or from general population samples. In addition, with small sample sizes, estimates of treatment effect have wide confidence intervals, creating additional uncertainty in cost-effectiveness findings.

But the greatest uncertainty comes from the availability of complete data for only one of four types of SMA. While it may be reasonable to assume that Spinraza's impact on motor function would be consistent across types, extrapolating these changes to longer-term outcomes would represent a major challenge. In addition, the high costs of Spinraza are likely to result in cost-effectiveness estimates that exceed commonly-cited thresholds in the US (i.e., $50,000 - $150,000 per QALY gained), even if

substantial cost offsets from reduced supportive care needs are realized. For example, at $375,000 per year, a complete offset of the estimated annual costs of supportive care ($120,000) would leave an incremental cost of $255,000 per extra year of life gained. In addition, Type 1 SMA is likely the population in which treatment would be demonstrated to be most cost-effective; severity is generally lower in the other types, so potential cost-offsets from reducing costs of supportive care are likely lower as well. As noted earlier in this technical brief, the application of traditional cost-effectiveness thresholds to treatments of rare and ultra-rare conditions is controversial and not used routinely as the sole method for judging the value of ultra-rare drugs in any country.

Methodologic Challenges in Assessing the "Value" of Treatments for Rare Diseases

Challenges with Epidemiologic and Clinical Evidence

The small populations available and other practical considerations discussed above often lead to difficulties in obtaining high-quality epidemiologic and clinical evidence on rare conditions and their treatments.[58-61] As was pointed out in a report from the 2016 ICER Membership Policy Summit:[61] "Other factors that complicate the generation of robust evidence include the lack of standard patient-centered outcome measures or surrogate measures for some genetic conditions; a lack of standardization of 'usual supportive care;' and novel mechanisms of action and viral vector techniques that raise questions about the long-term safety and durability of any early clinical benefits seen with gene therapies." Most of these factors would apply to some degree to the evaluation of treatments for many rare conditions.

Because of these challenges, the available evidence often provides less certainty in comparative clinical effectiveness than would be available for non-orphan therapies. There is therefore a heightened sense that for many orphan drugs, especially those approved on accelerated pathways, additional evidence generation after regulatory approval will be needed to gain additional certainty regarding the benefits and harms among various subpopulations.[59,61,62] Since a judgment regarding comparative clinical effectiveness is the foundation of any assessment of value, the greater uncertainty often associated with orphan drugs creates corresponding uncertainty within any subsequent analysis of cost-effectiveness over the short or long-term.[60,63] However, it has been suggested that society may be willing to tolerate greater uncertainty around the value of orphan drugs, because the potential risk from poor decisions is lower due to the smaller number of patients involved.[62]

Issues/Methodologic Concerns in Cost-Effectiveness Analysis of Orphan Drugs

Other aspects of rare diseases impact the feasibility of conducting and interpreting traditional cost-effectiveness assessments of orphan drugs.[64] First, the impact on quality of life is difficult to evaluate for treatments of diseases that affect infants and young children.[65] Quality of life with a condition, and the impacts of treatments on quality of life, are usually measured via patients' responses to questionnaires, which is not possible for infants and very young children. In such cases, the parents of affected infants (or other caregivers) may be proposed as proxies for the measurement of these patients' quality of life, although it is unknown how accurately such responses reflect patients' actual quality of life.[65]

A related issue is that such conditions will often have important quality-of-life impacts not only on the patients, but also on the family and other caregivers of such patients. The cost-per-QALY framework usually focuses on the quality of life of the individual patient only. However, as Prosser et al. have pointed out, this "does not preclude the inclusion of QOL effects for others (e.g., caregivers, family members). Alternative economic frameworks using the household as the unit of analysis have been proposed and merit further review."[65] However, this alternative approach has not been widely used, and would hinder comparisons with cost-effectiveness analyses that do not use this approach.

In addition, cost-effectiveness analysis uses patients' rating of quality of life in valuing the extension of life, which would mean that extension of life for patients with severe disability (and therefore worse quality of life) would result in higher (i.e., less favorable) cost-effectiveness ratios relative to patients with less disability, all else being equal. Ethical concerns have been raised that if cost-effectiveness evaluations are done without awareness of this issue, it may be viewed as discriminating against treatments for severe conditions, such as under-treated rare diseases. In such cases, it might be argued that QALY gains for patients with more severe disease should be given additional weight over those for patients with less severe disease. However, as McCabe et al. have pointed out, "The often cited objective of maximising health gains is consistent with the view that clinical need can be regarded as the capacity to benefit from an intervention and that every individual's health gain is valued equally. This view of need, and the implicit view of equity, is embedded in cost-effectiveness analysis. If the objective is to maximise health outcomes, the cost-effectiveness of drugs for rare diseases should be treated in the same way as that of other technologies."[62]

Even if these difficulties can be overcome or mitigated, and a good-quality cost-effectiveness analysis is conducted, there may be other concerns with applying the results to evaluations of rare disease treatments. Because of the small populations over which costs can be spread, and the often complex nature of rare diseases and their treatments, the cost per QALY for specific health care interventions may be relatively higher than similar interventions that treat more common conditions,[64] and would often not be considered cost-effective at commonly cited thresholds.[59] Picavet et al. analyzed results from published cost-effectiveness analyses for 19 orphan drugs, and found 61 incremental cost-effectiveness ratios that ranged from €6,311/QALY ($8,693/QALY) to €974,917/QALY ($1,342,861/QALY).[66] However, challenges with cost-effectiveness estimates for orphan drugs were not universally observed. The median incremental cost-effectiveness ratio was €40,242/QALY ($55,429/QALY), and the authors found that 10 of the 19 orphan drugs would be considered cost-effective at NICE's threshold of £30,000/QALY.

Proposed Approaches to Cost-Effectiveness Analysis of Orphan Drugs

These methodological and practical issues have led to alternative approaches to assessing interventions for rare diseases, including proposed modifications to standard cost-effectiveness methods. Below, we briefly describe some of the procedural and methodological changes that have been proposed to deal with these issues when evaluating the long-term value of drugs for rare conditions, including conditions affecting children.

One response has been simply to decide that the use of cost-effectiveness analysis is inappropriate as a guide for pricing or coverage decisions regarding orphan or ultra-orphan drugs, and to use other factors in making these decisions, such as level of unmet need or the innovative character of the treatment.[67] For example, countries such as Belgium and Turkey do not require pharmacoeconomic analyses in the assessment of orphan drugs.[60,68] Other researchers have accepted the usefulness of cost-effectiveness analysis in assessing orphan drugs, but have noted that different value standards could be used than for drugs that treat more prevalent diseases.[69] The various metrics proposed have taken several forms.

First, one approach that has been proposed is the use of different cost-effectiveness thresholds for orphan or ultra-orphan drugs.[59,66,70] The presumption is that this would better reflect the "principle that each person has a right of access to care"[70] or a societal preference for the treatment of rare diseases, through a greater willingness to pay for such treatments than for treatments for more common diseases. For example, decision-makers could use one willingness-to-pay threshold for most interventions considered, but choose to use a higher threshold for interventions that treat rare or ultra-rare conditions. One problem with this approach is that there is seldom an explicit rationale for the specific willingness-to-pay threshold that is selected, with little evidence that society's actual willingness to pay for such treatments is higher relative to those for more common conditions.[64,68] In addition, accepting a single higher threshold for all orphan or ultra-orphan drugs implies that society's willingness to pay is increased by the same amount for all rare conditions, with no variation by, for example, the rarity or severity of the disease.

Attempts to measure whether the public expresses preference for treatment of rare diseases over more prevalent ones have found weak or inconsistent preference for rarity.[59,60,64] For example, Desser et al. found no preference for treating rare over common diseases in a survey of Norwegian adults.[71] Wiss et al. recently found no preference for treatment of rare disease over common ones in a survey of a random sample of the Swedish population.[72] There is also an ethical implication of using different thresholds, in that this implies different valuations of health improvements for patients with rare diseases than for patients with common diseases.[62]

Second, some researchers have proposed specific variations on the QALY, as a way of preserving the overall cost-utility framework while acknowledging some of the difficulties of using traditional

quality-of-life or preference measures for calculating QALYs in rare conditions. One proposed variation is the use of "person trade-off" QALY estimation, in which respondents are asked to choose between different health states for a group of persons or a population.[1] In typical QALY measurement, a patient or other respondent is asked to imagine themselves being in two different health states, and to assess the relative value of spending time in health state A versus health state B. For person trade-off measures, the respondent is asked to choose between health states A and B for groups of patients, rather than for themselves. For example, rather than asking the respondent if they would choose a given number of months in health state A or one year in perfect health, the respondent might be asked how many lives saved of people in health state A they would consider equivalent to saving the lives of 100 healthy people. Research has shown that individuals may make different choices when doing so for oneself than when asked to imagine doing so for a population or group of patients, because "society's valuations of different outcomes are a function not only of the sum of individual utilities…but also of concerns for equity".[73] It is possible that decisions made using such a person trade-off framework might accord more value to interventions that treat populations with rare conditions than those made using a framework that only accounts for personal choices. However, the measurement of such "person trade-offs" is difficult, and this technique has rarely been used in practice.[73]

Another proposed variation is the use of equity-weighted QALY estimation.[68] In traditional QALY measurement, it is assumed that equivalent changes in quality of life are equally valued across patients. However, some have argued that societal decision-making should explicitly allow for equity considerations that could lead to differential weighting of health gains across individuals.[74] The suggestion is to multiply or inflate the QALYs gained for some patients, for example, if they have an especially severe condition or one that will be a lifelong burden. The rationale for inflating or giving extra weight to QALYS in some situations would be to reflect society's ideas of equity, or fairness. For example, one approach to this would be to count similar health improvements for those with rare diseases more highly than those for patients with more common conditions,[59,68,70] if that were thought to lead to a more equitable situation overall (e.g., because treatments for rare diseases are under-studied).

While these variations on the QALY may solve certain issues around the valuation of orphan drugs, they raise other ethical and practical concerns.[62] It is unclear whether metrics based on person trade-offs should be considered more relevant than those based on summations of individual preferences, even from a societal perspective. While weighting QALYs for equity may boost certain under-privileged groups, it must be recognized that it simultaneously decreases the valuation of treatments for other groups, such as those with more common diseases.[62,68] From a more practical standpoint, use of either technique would require the collection of data on population-weighted utilities or equity weights to apply to different populations. Capturing these societal values and mathematically using them to weight the QALYs gained from some treatments and not for others

would be controversial, because of the implied disadvantage for some patients that occurs any time other patients get special preference. To date, there has been no consensus that the use of these techniques is warranted,[62] and their use in economic evaluations has been negligible.[59,70]

Beyond Cost-Effectiveness Calculations: The Role of Contextual Factors

Some health economists have pointed out that there are always value considerations that go beyond cost-per-QALY calculations 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.[59]   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 as well as common conditions.[62]

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 non-quantified 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.[64,70]

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.[70,75] 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 see a need to explicitly include a domain for access to health care interventions. Other domains that are often mentioned as not being adequately captured in existing clinical and economic evaluations include consideration of the value of hope and the value of innovation *per se*.[64] Other domains might consider one or more of the ethical considerations listed above 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.[62]

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 and Kanavos 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.'"[64] At the other end of the analytic spectrum, multi-criteria decision analysis (MCDA) may be utilized, where the values assigned to each domain and the weights used to combine them are determined through a formal process, and made explicit and public.[60,70,76] 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 MCDA 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.[76] 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.[59]

Key Questions for Discussion at the ICER Summit

Panelists representing several different stakeholder viewpoints, including patients, clinicians, manufacturers, ethicists, health economists, and payers, will discuss the following key issues at the Orphan Drug Assessment and Pricing Summit on May 31, 2017. Key considerations and guiding principles will be summarized following the meeting.

Issue 1: Contextual Considerations and Ethical Issues

What is an ultra-orphan drug? What are the ethical considerations for and against giving special treatment to clinical and value assessments of ultra-orphan drugs?

> Moderator will facilitate a conversation that touches on certain additional considerations related to treatments for rare conditions from a societal and ethical perspective, and how they should influence the judgments of strength of evidence and analysis of reasonable long-term value for money. Considerations may include:
>
> o   First-ever treatments for serious illnesses
> o   Preferences for illnesses of children
> o   Environment/incentives to support investment in future treatments

Issue 2: Comparative Clinical Effectiveness

ICER has a standard approach for judging net health benefit of new treatments. Should that approach change for ultra-orphan drugs? If yes, how? If no, why not?

Moderator will facilitate a discussion that touches on key considerations such as:

- Small clinical trial populations
- Different types and quantities of evidence / Accelerated approval pathway
- Use of surrogate outcomes
- Durability of effect
- How do the above impact assessment of clinical effectiveness?

Issue 3: Other Benefits or Disadvantages

ICER has a standard approach to discussing and identifying other benefits or disadvantages of new treatments. Do ultra-orphan drugs require a change to this approach, or another approach altogether?

Moderator will facilitate a discussion that touches on key considerations such as:

- Circumstances and conditions that surround many rare conditions, such as unmeasured patient health benefits, benefits that take years to measure, or caregiver burden
- How to weigh the above in the assessment of value of ultra-orphan drugs

Other Benefits or Disadvantages may include:

- Direct patient health benefits that are not adequately captured by the QALY
- Reduced complexity that will significantly improve patient outcomes
- Reduction of important health disparities across racial, ethnic, gender, socio-economic, or regional categories
- Significant reduction of caregiver burden
- Novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments
- Significant impact on improving return to work and/or overall productivity

Issue 4: Price, Cost-effectiveness, and Affordability

ICER has a standard approach to cost-effectiveness analysis (long-term value for money) and potential budget impact (affordability). Do these approaches need to change for ultra-orphan drugs? If so, how should they change?

Moderator will facilitate a discussion that touches on key considerations such as:

- The role of cost of development, cost-effectiveness, and potential budget impact in assessing value for ultra-orphan treatments
    - Are development and manufacturing costs relevant to pricing and assessment of value?
    - What is the role of cost-effectiveness analysis using cost/QALY thresholds? Do we need different thresholds for (ultra)orphan treatments?
    - Do small patient populations justify high prices?

- Good value but not affordable? What should the role of potential budget impact be in considerations of pricing, coverage, and payment?

References

1. Disorders NOfR. 2017; https://rarediseases.org/nord-and-trio-health-provide-insights-improve-access-and-quality-care-more-than-7000-rare-diseases/. Accessed May 5, 2017.

2. Pharmaceutical Research and Manufacturers of America. Rare Diseases: A Report on Orphan Drugs in the Pipeline. In: America PRaMo, ed2013.

3. Hughes DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? *QJM : monthly journal of the Association of Physicians.* 2005;98(11):829-836.

4. Largent EA, Pearson SD. Which orphans will find a home? The rule of rescue in resource allocation for rare diseases. *The Hastings Center report.* 2012;42(1):27-34.

5. Cookson R, McCabe C, Tsuchiya A. Public healthcare resource allocation and the Rule of Rescue. *Journal of medical ethics.* 2008;34(7):540-544.

6. Kesselheim AS, Treasure CL, Joffe S. Biomarker-Defined Subsets of Common Diseases: Policy and Economic Implications of Orphan Drug Act Coverage. *PLoS medicine.* 2017;14(1):e1002190.

7. US Food and Drug Administration. *2016 Novel Drugs Summary.* Silver Spring, MD: US Food and Drug Administration; January 2017 2017.

8. Richter T, Nestler-Parr S, Babela R, et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2015;18(6):906-914.

9. Agency EM. Orphan Designation. 2017; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac0580b18a41. Accessed May 5, 2017.

10. Kanavos P, Nicod E. What is wrong with orphan drug policies? Suggestions for ways forward. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2012;15(8):1182-1184.

11. C. L. *NICE and NHS England consultation on changes to the arrangements for evaluating and funding drugs and other health technologies assessed through NICE's*

technology appraisal and highly specialised technologies programmes.: National Institute for Health and Care Excellence; March 15 2017 2017.

12. Griggs RC, Batshaw M, Dunkle M, et al. Clinical research for rare disease: opportunities, challenges, and solutions. *Molecular genetics and metabolism.* 2009;96(1):20-26.

13. Winquist E, Coyle D, Clarke JT, et al. Application of a policy framework for the public funding of drugs for rare diseases. *Journal of general internal medicine.* 2014;29 Suppl 3:S774-779.

14. Broome J. Trying to value a life. *Journal of Public Economics.* 1978;9:91-100.

15. Jena A, D. L. Value frameworks for rare diseases: should they be different? 2017; http://healthaffairs.org/blog/2017/04/12/value-frameworks-for-rare-diseases-should-they-be-different/. Accessed May 5, 2017.

16. Rivlin MM. Why the fair innings argument is not persuasive. *BMC medical ethics.* 2000;1:E1.

17. Landfeldt E, Lindgren P, Bell CF, et al. The burden of Duchenne muscular dystrophy: an international, cross-sectional study. *Neurology.* 2014;83(6):529-536.

18. Herder M. What Is the Purpose of the Orphan Drug Act? *PLoS medicine.* 2017;14(1):e1002191.

19. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *Jama.* 2011;305(22):2320-2326.

20. Grassley C HO, Cotton T. Letter to Hon. Gene Dodaro, Comptroller General. In: Office GA, ed2017.

21. Handfield R, Feldstein J. Insurance companies' perspectives on the orphan drug pipeline. *American health & drug benefits.* 2013;6(9):589-598.

22. Young K RR, Garfield R, Musumeci M. Medicaid's most costly outpatient drugs. 2016; http://kff.org/report-section/medicaids-most-costly-outpatient-drugs-issue-brief/. Accessed May 5, 2017.

23. Markus AR, West KD. Defining and determining medical necessity in Medicaid managed care. *Pediatrics.* 2014;134(3):516-522.

24. Settlement reached over medicaid coverage of cystic fibrosis drug: Arkansas federal court case highlights medical necessity, high cost of targeted therapies. *American journal of medical genetics Part A.* 2015;167a(4):viii-ix.

25. Greissing J. Coverage of Rare Disease Therapies in Medicaid and Medicare and the Impact on Patient Care. 2016.

26. Sandman L, Gustavsson E. The (Ir)relevance of Group Size in Health Care Priority Setting: A Reply to Juth. *Health care analysis : HCA : journal of health philosophy and policy.* 2017;25(1):21-33.

27. Tordrup D TV, Kanavos P. Orphan drug consiserations in Health Technology Assessment in eight European countries. *Rare Diseases and Orphan Drugs.* 2014;1(3):83-95.

28. Lofgren J. Pricing uncertainty for orphan drugs and innovative new drugs. 2015; http://www.lindahl.se/media/1014453/Pricing_uncertainty_for_orphan_drugs_and_innovative_new_drugs.pdf. Accessed May 5, 2017.

29. Buruma S. *The Netherlands: All Eyes on Pharmaceutical Expenditures in the Hospital Sector.*: Axon Healthcare; September 2015 2015.

30. Winquist E, Bell CM, Clarke JT, et al. An evaluation framework for funding drugs for rare diseases. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2012;15(6):982-986.

31. Blackburn H, Labarthe D. Stories from the evolution of guidelines for causal inference in epidemiologic associations: 1953-1965. *American journal of epidemiology.* 2012;176(12):1071-1077.

32. Ontario Public Drug Programs. Elaprase (idursulfase) -- Reimbursement Guidelines. In: Programs OPD, ed: Ontario Ministry of Health and Long-Term Care; 2011.

33. Grant K. Rare public hearing highlights concerns over explosion of high-priced specialty drugs in Canada. *The Globe and Mail*2017.

34. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *European journal of human genetics : EJHG.* 2012;20(1):27-32.

35. Gregoretti C, Ottonello G, Chiarini Testa MB, et al. Survival of patients with spinal muscular atrophy type 1. *Pediatrics.* 2013;131(5):e1509-1514.

36. Prior TW, Finanger E. Spinal Muscular Atrophy. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews(R)*. Seattle (WA): University of Washington, Seattle. 1993.

37. SMA Foundation. About SMA. 2017; http://www.smafoundation.org/about-sma/. Accessed May 5, 2017.

38. Finkel R, Bertini E, Muntoni F, Mercuri E. 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. *Neuromuscular disorders : NMD.* 2015;25(7):593-602.

39. Bach JR. Avoiding respiratory failure in neuromuscular disease: why is it not done? *American journal of physical medicine & rehabilitation.* 2007;86(3):222-224.

40. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. *The Lancet Neurology.* 2012;11(5):443-452.

41. Lewin Group. *Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States.* Lewin Group;2012.

42. Biogen Idec. Spinraza (nusinersen) prescribing information. 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf. Accessed May 5, 2017.

43. Finkel R. Primary Efficacy and Safety Results From the Phase 3 ENDEAR Study of Nusinersen in Infants Diagnosed With Spinal Muscular Atrophy (SMA). Paper presented at: 43rd Annual Congress of the British Paediatric Neurology Association; January 11-13, 2017, 2017; Cambridge, UK.

44. Finkel R. Efficacy and safety of nusinersen in children with later-onset spinal muscular atrophy (SMA): interim results of the phase 3 CHERISH study. American Academy of Neurology; April 24, 2017, 2017; Boston, MA.

45. Final Phase 3 Study Data Show SPINRAZA® (nusinersen) Significantly Improved Motor Function in Children with Later-Onset Spinal Muscular Atrophy [press release]. 2017.

46. Sarepta. Exondys 51 (eteplirsen) prescribing information. 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf. Accessed May 5, 2017.

47. Genzyme. Myozyme (alglucosidase alfa) prescribing information. 2006; https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125141s219lbl.pdf. Accessed May 5, 2017.

48. Genzyme. Cerezyme (imiglucerase) prescribing information. 2005; https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/20367s066lbl.pdf. Accessed May 5, 2017.

49. Shire. VPRIV (velaglucerase) prescribing information. 2010; https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022575lbl.pdf. Accessed May 5, 2017.

50. Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *The Journal of pediatrics.* 2006;148(5):671-676.

51. Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. *Drug design, development and therapy.* 2017;11:533-545.

52. Stirnemann J, Belmatoug N, Camou F, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. *International journal of molecular sciences.* 2017;18(2).

53. Ciana G, Addobbati R, Tamaro G, et al. Gaucher disease and bone: laboratory and skeletal mineral density variations during a long period of enzyme replacement therapy. *Journal of inherited metabolic disease.* 2005;28(5):723-732.

54. Anthem. Nusinersen Medical Policy. 2017; https://www11.anthem.com/ca/medicalpolicies/policies/mp_pw_c194560.htm. Accessed May 5, 2017.

55. Humana. Nusinersen Medical Precertification Form. 2017; http://apps.humana.com/marketing/documents.asp?file=3096405. Accessed May 5, 2017.

56. Aetna. Nusinersen Medical Policy. 2017; http://www.aetna.com/cpb/medical/data/900_999/0915.html. Accessed May 5, 2017.

57. United HealthCare. Nusinersen Medical Policy. 2017; https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Prot

ocols/Medical%20Policy%20Update%20Bulletins/Policy%20Update%20Bulletins/2017/Medical_Policy_Up date_Bulletin_February_2017.pdf. Accessed May 5, 2017.

58.   Rawson NS. Health technology assessment of new drugs for rare disorders in Canada: impact of disease prevalence and cost. (1750-1172 (Electronic)).

59.   Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet journal of rare diseases.* 2011;6:42.

60.   Zelei T, Molnar MJ, Szegedi M, Kalo Z. Systematic review on the evaluation criteria of orphan medicines in Central and Eastern European countries. *Orphanet journal of rare diseases.* 2016;11(1):72.

61.   Marsden G TA, Pearson SD, Dreitlein B, Henshall C. *Gene Therapy: Understanding the Science, Assessing the Evidence, and Paying for Value.* Boston, MA: Institute for Clinical & Economic Review; March 2017 2017.

62.   McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the NHS: should we value rarity? *BMJ (Clinical research ed).* 2005;331(7523):1016-1019.

63.   Winstone J, Chadda S, Ralston S, Sajosi P. Review and comparison of clinical evidence submitted to support European Medicines Agency market authorization of orphan-designated oncological treatments. *Orphanet journal of rare diseases.* 2015;10:139.

64.   Nicod E, Kanavos P. SCIENTIFIC AND SOCIAL VALUE JUDGMENTS FOR ORPHAN DRUGS IN HEALTH TECHNOLOGY ASSESSMENT. *International journal of technology assessment in health care.* 2016;32(4):218-232.

65.   Prosser LA, Hammitt Jk Fau - Keren R, Keren R. Measuring health preferences for use in cost-utility and cost-benefit analyses of interventions in children: theoretical and methodological considerations. (1170-7690 (Print)).

66.   Picavet E, Cassiman D, Simoens S. What is known about the cost-effectiveness of orphan drugs? Evidence from cost-utility analyses. *Journal of clinical pharmacy and therapeutics.* 2015;40(3):304-307.

67.   Picavet E, Cassiman D, Simoens S. Reimbursement of orphan drugs in Belgium: what (else) matters? *Orphanet journal of rare diseases.* 2014;9:139.

68.   Dupont AG, Van Wilder PB. Access to orphan drugs despite poor quality of clinical evidence. *British journal of clinical pharmacology.* 2011;71(4):488-496.

69.   Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. *International journal of technology assessment in health care.* 2007;23(1):36-42.

70.   Simoens S, Picavet E, Dooms M, Cassiman D, Morel T. Cost-effectiveness assessment of orphan drugs: a scientific and political conundrum. *Applied health economics and health policy.* 2013;11(1):1-3.

71.   Desser AS, Gyrd-Hansen D, Olsen JA, Grepperud S, Kristiansen IS. Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67. *BMJ (Clinical research ed).* 2010;341:c4715.

72.   Wiss J, Levin LA, Andersson D, Tinghog G. Prioritizing Rare Diseases. *Medical decision making : an international journal of the Society for Medical Decision Making.* 2017:272989x17691744.

73.   Nord E. The person-trade-off approach to valuing health care programs. (0272-989X (Print)).

74.   Sheehan M. Orphan drugs and the NHS: fairness in health care entails more than cost effectiveness. *BMJ (Clinical research ed).* 2005;331(7525):1144-1145.

75.   Paulden M, Stafinski T, Menon D, McCabe C. Value-based reimbursement decisions for orphan drugs: a scoping review and decision framework. *PharmacoEconomics.* 2015;33(3):255-269.

76.   Walker A. Challenges in Using MCDA for Reimbursement Decisions on New Medicines? *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2016;19(2):123-124.