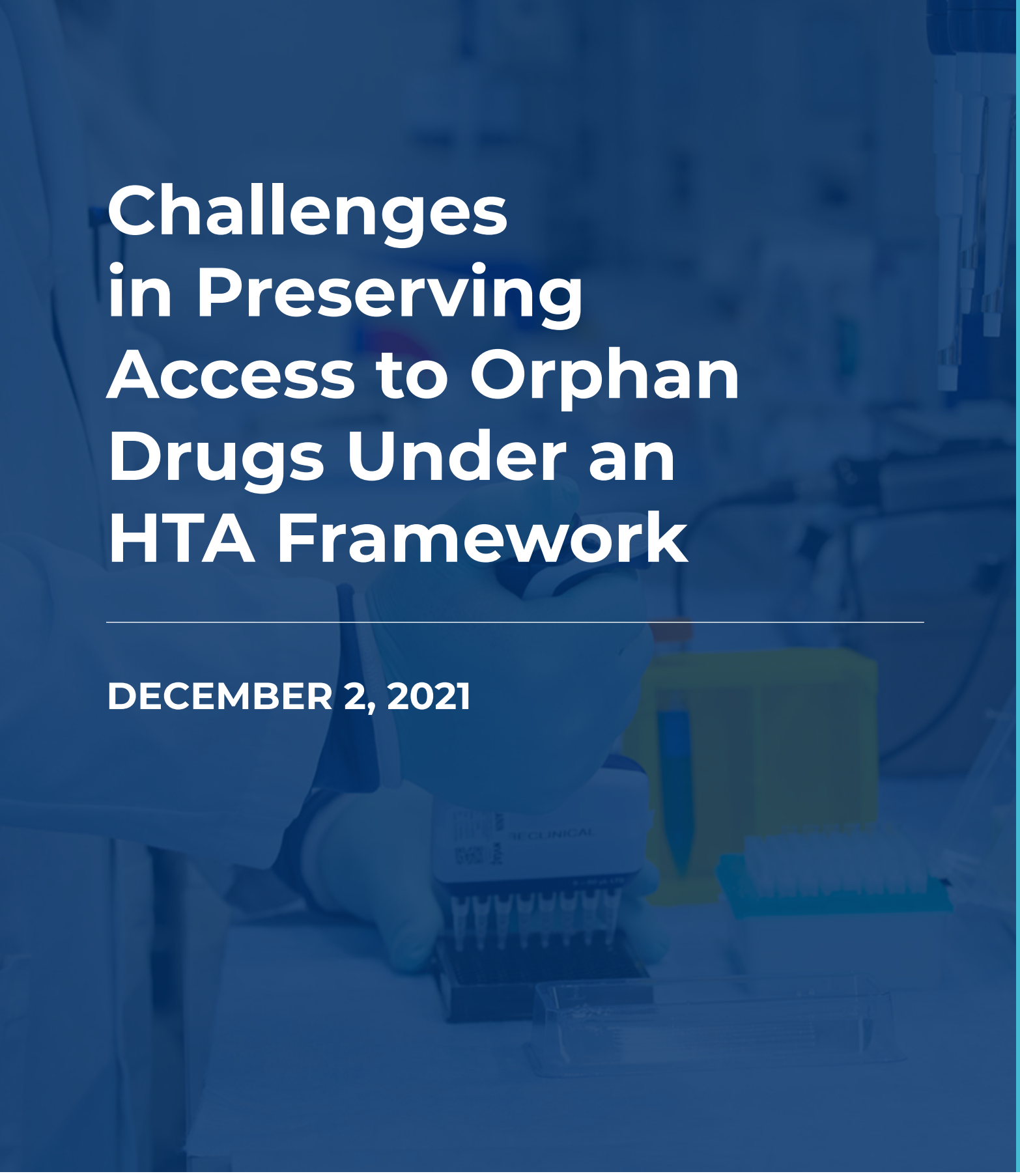

Challenges in Preserving Access to Orphan Drugs Under an HTA Framework

DECEMBER 2, 2021

ALEXION®
AstraZeneca Rare Disease

CONTENTS

EXECUTIVE SUMMARY

Under pressure to address rising health care costs for American families, policymakers in the U.S. are increasingly looking overseas for potential policy remedies, particularly with respect to drug pricing. Advocates for establishing a national health technology assessment (HTA) body in the U.S. argue that such systems enable payers to set coverage and reimbursement policies based on a treatment's value to patients and society. While placing a dollar value on life across diverse patient populations remains controversial generally, HTA's one-size-fits-all approach may be particularly problematic when it comes to orphan drugs developed to treat rare disease.

Assessment practices by HTA bodies around the world were created to evaluate widely used medical technologies and do not fully account for the unique value proposition of orphan drugs, which provide significant clinical benefits to the millions of Americans afflicted with rare disease. For this reason, few HTA bodies use standard assessment practices for orphan drugs. Instead, for orphan drug evaluations, most HTA bodies provide targeted exceptions to their value assessment policies. These exceptions may include:

- Assumed benefit thresholds – Allow approved orphan drugs that remain below a certain cost threshold to be automatically deemed beneficial to patients—meaning that HTA bodies cannot issue a negative reimbursement decision.
- Specialized HTA pathways – Offer a more flexible approach to evaluating pharmaceuticals for rare disease and increase the willingness to pay threshold to accommodate increased costs.
- Higher willingness to pay thresholds – Place a higher willingness to pay threshold for health gains accruing to patients with rare diseases.
- Pre-authorization programs – Allow certain orphan drugs to receive reimbursement decisions prior to market authorization.

Even with these exceptions, in practice, patient access to treatments is restricted under HTA. Based on the Center for Healthcare Economics and Policy's analysis of access and outcomes in countries with centralized, government-run HTA bodies, we find the process has the potential to delay or deny access to treatment for those living with rare disease through inadequate reimbursement and pricing recommendations. HTAs may not only limit access to existing treatments, but could also significantly decrease the likelihood of new orphan drugs coming to market, denying patients with rare disease the hope of future treatment.

Key Findings

- HTA practices are designed to be used for medical technologies and pharmaceuticals that treat commonly-occurring diseases, and are not fit to determine the value of orphan drugs for rare disease, which face unique challenges.[1]
- Estimating the value or clinical improvement for orphan drugs is complicated by small patient groups, making it difficult for HTA bodies to precisely estimate clinical and economic value and set a value-based price.[2]
- Standard HTA that uses value-based price evaluation does not properly account for the value of orphan drugs for rare disease patients, especially when they are the only treatment for a given disease. Instead, health gains are treated the same for all patients regardless of disease severity.[3]
- Standard European HTAs have effectively restricted access to orphan drugs, delaying or denying access to treatment for rare disease.[4] While many countries with HTA bodies offer orphan drugs special considerations in the assessment process, these accommodations are often insufficient to overcome the challenges of applying the HTA framework to orphan drugs.

- Quality-Adjusted Life Years (QALYs), the most commonly used tool to assess a drug's value through the HTA process, fail to measure many of the life-altering benefits that orphan drugs bring.[5] As a result, HTA bodies are more likely to deem orphan drugs unworthy of their price and reliance on QALYs could restrict the number of orphan drugs that come to market.
- Cost-effectiveness considerations may result in low reimbursement rates for orphan drugs. The use of price thresholds in any capacity creates a disincentive for rare disease research by cutting into manufacturers' return on investment.[6]
- If the U.S. were to model a national HTA body based on the practices of the Institute for Clinical and Economic Review (ICER), access to orphan drugs could be severely curtailed. As of 2020, all orphan drugs in the U.S. received a negative ICER assessment.[7]
- The value assessment frameworks that many HTA bodies employ do not take into account the benefits new medical technologies may provide in terms of reducing health disparities among racial and ethnic minority groups.[8,9]
- The HTA value assessment framework may inadvertently perpetuate health disparities by undervaluing certain benefits, such as the diminution of burdensome side effects of existing treatment alternatives, that improve both quality of life and health outcomes – particularly in Black patients.[10]

BACKGROUND: RARE DISEASE IN THE U.S.

Despite the low prevalence of individual rare diseases, up to 30 million Americans (1 in 10) are afflicted by 7,000 known rare conditions.[11] Rare diseases, defined by the Food and Drug Administration (FDA) as conditions that impact fewer than 200,000 patients nationwide, are by nature under-researched, under-diagnosed, and under-treated. Due in part to a lack of treatments, approximately 37 percent of rare disease patients have reduced life expectancies and one-quarter die before they reach the age of five.[12] Compounding the physical toll of disease, the stress of inadequate treatment and the frustration of having to modify one's routines and relationships increases the prevalence of mental health conditions among those afflicted with rare disease.[13] Despite the suffering that rare diseases often bring, there were few available treatments for rare diseases until the 1980s. Even today, 95 percent of rare diseases have no treatment option.[14]

Facing pressure from rare disease patients and advocates, Congress passed the Orphan Drug Act in 1983 to incentivize the development of new treatments for people with rare diseases. The law provides tax credits of up to 50 percent for research and development and a seven-year period of market exclusivity for orphan drugs—those designated to treat a rare disease or condition.[15] Following passage of the Orphan Drug Act, the FDA approved more than 400 rare disease therapies, compared to a meager 34 approvals prior to the law's enactment.[16] A bevy of rare disease innovations developed in the wake of the law revolutionized health outcomes for rare disease patients, underscoring the importance of a tailored approach to regulating orphan drugs.

The benefits of innovation in orphan drugs is not limited to rare disease patients, however. In 2018, the FDA approved patisiran, approved as ONPATTRO®, which halts or even reverses the progression of familial amyloid polyneuropathy (FAP), a progressive, sometimes fatal hereditary disease that can cause a loss of nerve function in the periphery of the body as well as in involuntary autonomous functions such as heart beat and blood pressure.[17] The discovery was groundbreaking for the one in 100,000 Americans suffering from the rare disease,[18] but its development had implications beyond the treatment of FAP: mRNA vaccines on the market today to prevent COVID-19 rely on a drug delivery system similar to that of Onpattro's.[19]

However, as the number of orphan drugs approved in the U.S. increases steadily, policy experts are keeping a close eye on pricing. While orphan drugs, like Onpattro, have dramatically improved patient health outcomes, these treatments are marketed to inherently small patient populations, requiring life sciences companies to seek high prices to cover research and development costs. As a result, orphan drugs are often priced higher per patient than treatments for more prevalent conditions. A 2015 report found that the average cost of orphan drugs in the U.S. was $111,820 in 2014, compared to $23,331 for pharmaceuticals that treat more common diseases.[20] Many health plans turn to reinsurance mechanisms, orphan drug carve outs, and separately funded risk pools to help maintain the affordability of orphan drugs.[21]

Amidst concerns that orphan drugs could contribute to rising health care costs, some are now advocating for the establishment of a national, government-funded HTA body in the U.S., which would determine whether the value of a pharmaceutical warrants its price. In this report, we explore the methodological challenges associated with applying HTA-based value assessment to orphan drugs based on an analysis of HTAs in Europa and Asia, and outline specific considerations with respect to rare disease patient populations.

HISTORY OF THE HTA

HTAs were created to slow growing drug costs by performing evaluations that determine whether the cost of innovations in modern medicine outweigh their benefit, ultimately making recommendations for reimbursement and/or pricing.[22] HTAs originated in the U.S. in the 1970s in the U.S. Office of Technology Assessment (OTA) as part of a push to include more scientific evidence in health care. The OTA was defunded—and subsequently disbanded—in 1995, however, as drug prices continued to rise across the globe, other countries established centralized HTA bodies with broad power to determine pricing and access.[23] Through the 1980s, the concept of HTA was popularized in Europe and in Latin America and Asia two decades later.[24] Today, there are more than 40 HTA bodies around the world with discrete jurisdictions, all of which employ varying processes and techniques to assess pharmaceuticals and technologies.[25]

Each HTA body employs different practices, but medical technologies generally undergo the same three phases in the HTA process:[26]

1. **Assessment (evidence review):** The HTA body collects and reviews scientific evidence of the pharmaceutical's clinical benefits.
2. **Appraisal (evaluation):** A committee will review evidence of the pharmaceutical's benefits—clinical, economic and otherwise—to make a recommendation regarding reimbursement and/or pricing. In this step, the HTA body will seek to determine whether the drug provides sufficient benefit to merit its cost.
3. **Decision-Making (value, pricing, and reimbursement):** The relevant decisionmakers—whether that be a government agency or individual insurance providers—implement the HTA body's recommendation with respect to drug pricing and/or coverage. In this step, the relevant decisionmakers decide whether to cover the pharmaceutical, and if so, at what price.

Clinical benefit assessment decisions vary by country, but typically range from the most negative result, "contains no additional benefit," to the most positive, "contains substantial additional benefit," with numerous potential decision levels in between.[27]

In calculating the value of a new health technology or pharmaceutical, HTA bodies typically consider its medical, ethical, economic, and social repercussions.[28] A foundational element of the majority of these value assessments is cost-effectiveness analysis (CEA), which compares the cost of a new health technology to the estimated benefits it would provide patients and stakeholders.[29] Decisionmakers may set a CEA threshold when evaluating new medical technologies, which is equivalent to the maximum amount of money they would be willing to spend per unit of health gained. These "units" are often measured in quality adjusted life years (QALYs), which seek to measure how much certain medical treatments lengthen and improve patients' lives year by year. In so doing, HTA bodies can reduce spending on medical technologies they determine do not provide sufficient benefit compared to their cost; technologies whose cost falls below the willingness to pay threshold are considered cost-effective and worth reimbursing, whereas those whose cost per unit of health gained is above the threshold are considered poor value for the price. Although HTA bodies typically follow this general process, the minutiae of their assessment policies and procedures diverge significantly. Final HTA recommendations vary around the world, resulting in different reimbursement decisions for the same technologies, and varying levels of access.[30]

The process for orphan drug evaluation varies even more dramatically across different HTA bodies. While some make exceptions to the standard HTA evaluation methodology, others lack a special framework for evaluating orphan drugs, which are subject to unique pricing considerations and tend to offer different value to patients relative to other pharmaceuticals. This one-size-fits all approach is detrimental for the evaluation of orphan drugs, which are critical to addressing the unmet medical needs of vulnerable patient populations.

"[A] one-size-fits all approach [to HTA] is detrimental for the evaluation of orphan drugs, which are critical to addressing the unmet medical needs of vulnerable patient populations."

ORPHAN DRUGS, RARE DISEASE, AND THEIR CHALLENGES

Despite advancements since the passage of the Orphan Drug Act, U.S. patients with rare disease continue to experience barriers to diagnosis, care and treatment. Since individual rare diseases affect very few patients, many physicians never encounter patients with a particular rare disease and are therefore unfamiliar with its clinical manifestations. Diagnosing these conditions often requires multiple evaluations including genetic testing, physical examinations, and family evaluations—all of which can be costly and time consuming, delaying the diagnosis even further. In the U.S., 28 percent of rare disease patients said it took seven or more years to receive a diagnosis.[31] In low-income countries abroad, the average time-to-diagnosis is even longer.[32]

The heterogeneity of rare disease often poses challenges to accurate diagnosis, clinical research, and access to treatment—particularly for racial and ethnic minority groups. Disparities in disease prevalence and outcomes often have multiple explanations, including both biological differences and the effects of racial discrimination in the health care system."[33] For instance, lupus nephritis, an autoimmune kidney disease that can lead to kidney failure,[34] disproportionately affects Black patients, who also experience lower rates of renal survival[35] (38 percent) compared to white patients (68 percent).[36] In other cases, the reason behind the heterogeneity is not well understood. Kawasaki disease, which involves inflammation of the blood vessels, primarily impacts people of Asian and Pacific Island descent; however, the potential genetic factors behind its prevalence are not clear.[37]

Many rare diseases also manifest heterogeneously: patients may experience different disease progression, disease severity, and symptoms for the same affliction.[38] "In fact, 60 percent of rare diseases manifest with significant heterogeneity,"[39] which can vary across gender, race, ethnicity, and other demographic and physiological factors. Black patients with myasthenia gravis (MG), for example, experience disease onset approximately 18 years earlier than white patients.[40] This discrepancy in disease manifestation can present further challenges by complicating physicians' efforts to identify the disease.

Even after Americans with rare diseases are diagnosed, many experience significant barriers to initiating treatment. In fact, fewer than five percent of rare diseases have an FDA-approved treatment option.[41] Despite an increase in rare disease research funding in the past several decades, a substantial amount of further rare disease research is needed to find more treatments. Given that rare diseases affect few patients, other, more common diseases such as cancer, diabetes, and cardiovascular disease receive far more research funding. Between the lack of research funding and the possibility of a poor return on investment, few orphan drugs are made available each year, leaving rare disease patients with few to no available treatment options.

Even when a rare disease therapy is available, the out-of-pocket cost to patients can be prohibitive. In order to generate sufficient returns on investment despite small patient populations, orphan drugs are priced higher compared to common treatments and generics. While the average annual orphan drug cost is $32,000,[42] orphan drugs come with a wide range of price tags, some even extending into the millions of dollars. In the U.S., approximately 39 percent of pharmaceuticals with orphan indications cost more than $100,000 per year.[43] Patients may be forced to absorb much of these costs out-of-pocket. Out-of-pocket costs for orphan drugs are particularly high for children, and are on the rise; average annual out-of-pocket spending for orphan drugs rose from $486 to $866 between 2013 and 2018.[44]

Without these elevated prices, however, life sciences firms would be unable to finance the research and development process needed to verify a treatment's safety and efficacy. A typical new pharmaceutical product costs more than $2 billion to bring to market.[45] While HTA may aim to govern the use of society's resources, it is ill-suited for encouraging investments in research and development for rare diseases.

CHALLENGES IN APPLYING VALUE ASSESSMENT TO ORPHAN DRUGS

Various challenges prevent HTA bodies from appropriately measuring the value—and value-based price—for orphan drugs. First, measuring the precise clinical value of orphan drugs is often more challenging than is the case for more standard technologies. Second, even if the clinical benefits of orphan drugs could be measured precisely, there are conceptual challenges of measuring the economic value of these treatments.

Estimates of the value of clinical improvements for orphan drugs are more difficult to measure than standard therapies.

Sample Size

A crucial part of HTAs is the review of clinical evidence of a drug's efficacy; however, given that most rare diseases are under-researched, orphan drug makers often struggle to submit evidence that is deemed sufficient by HTA bodies.[46] While HTA bodies accept multiple study designs, most express a preference for large clinical trials. Reviewers consider large clinical trials to have more statistical power, meaning they can conclude that the study results are representative of an entire population of patients with a condition. However, one of the greatest challenges to measuring the clinical improvements provided by orphan drugs is small sample sizes for rare disease clinical trials. Given that rare diseases, by definition, afflict few people, it can be difficult to find enough participants for clinical trials. Delayed diagnoses may prevent researchers from identifying patients with rare disease, while unspecific diagnostic coding systems used in electronic health records and health insurance claims data can make these patients difficult to identify.[47] Geographic limitations also exacerbate limited sample sizes and varying levels of disease awareness, diagnosis, and prevalence in different locales may further limit the number of potential trial participants.[48]

In addition to these implications, small sample sizes threaten researchers' ability to complete rare disease trials at all, given that there are often very few potential study recruits. Studies with small sample sizes are more likely to be skewed by statistical outliers, sometimes resulting in a false positive or false negative result.[49] According to a 2019 study that analyzed 659 rare disease clinical trials, about 30 percent of those trials were discontinued[50] with one-third of the discontinued trials citing lack of patient accrual as the primary reason for discontinuation.[51] Furthermore, the dearth of potential study participants compromises the perceived integrity of the experiment, rendering their safety and efficacy findings less reliable from the perspective of an HTA.

Study Design

To accommodate for the challenge of small sample sizes, orphan drugs often employ non-randomized study designs to best measure their value. HTA bodies

and reviewers typically regard randomized controlled trials (RCT)—in which patients are randomly assigned to either a group receiving the treatment or a control group —as the gold standard of drug trial design. The control group can be a placebo or can be the old standard of care treatment. This approach is generally preferred as including a control group helps to eliminate biases that may compromise the study findings.[52] Due to a lack of participants, however, rare disease clinical trials often opt out of using traditional study designs in favor of designs that rectify the challenges of small sample sizes, which may cause HTA bodies to question the validity of any benefits that clinical trials may find. Some of these non-traditional methods often include non-randomized trials and single arm studies, which do not include a control group.[53] A study of clinical trials for 64 orphan drugs found that 35 percent utilized non-randomized trials and 30 percent lacked a control arm.[54] In addition to validity concerns, some believe that offering a placebo to rare disease patients when there is a lack of effective and safe original treatments may be unethical. These non-traditional study designs cause HTA bodies to doubt the findings' validity, sometimes leading to less favorable HTA outcomes.

Surrogate Endpoints

Many orphan drug trials rely on surrogate endpoints—biomarkers substituted for clinical outcomes of most interest to patients—in order to allow for earlier drug access.[55,56] By using a surrogate, researchers can measure treatment efficacy within a clinical trial setting more quickly, leading to the earlier approval of life-changing new medical technologies. While many orphan drug trials employ surrogate endpoints to deliver treatments to patients that have no other options, some HTA bodies argue that measuring another outcome as a proxy for the true desired outcome, such as overall survival, lowers the quality of the trial's evidence. Furthermore, it can prove challenging for rare disease drugs to replicate surrogate findings with real world findings due to small sample sizes. In a 2021 study, HTA bodies either rejected or granted restricted approval of 72 percent of drugs that used surrogate endpoints.[57]

Consider, for instance, Fabry disease—a rare genetic disorder in which the accumulation of globotriaosylceramide (Gb3), a part of the cell membrane, is associated with organ damage that can lead to stroke, heart attack, and kidney failure.[58] Fabry disease affects 1 in 50,000 men in the U.S., but prevalence amongst women remains unknown.[59] Disease progression in Fabry disease is often slow and it could take years or even decades to measure clinical endpoints such as survival or time to heart attack or stroke. To more quickly assess whether a new medical technology could improve outcomes for patients with Fabry disease, scientists have used the reduction or elimination of Gb3 in certain cells as an appropriate surrogate endpoint for clinical improvement. Specifically, agalsidase beta was granted accelerated approval in 2003 for the treatment of Fabry disease based on its ability to reduce Gb3 levels. Later, researchers were able to show that the treatment provided "significant clinical benefit by reducing the risk of a major clinical event."[60]

Patient-Reported Outcome Measures

Reporting disease-specific patient-reported outcomes (PROs) is challenging for rare diseases, causing HTAs to make decisions that may not always benefit individuals. Patient-reported outcome measures (PROMs) measure patients' experience with their disease and treatment to convey a more comprehensive understanding of a treatment's impact on quality of life and other factors beyond the direct clinical results.[61] Disease-specific PROMs are particularly useful because they capture the unique issues experienced by specific patient populations; as a result, the FDA and various HTA bodies have supported the proliferation of more patient-centric measures in clinical trials in recent years.[62,63]

When it comes to rare disease, however, it is hard to develop reliable, disease-specific PROMs. Due to the inherently small sample sizes of orphan drug clinical trials, "it is difficult for HTA bodies and payers to accept the results that can be realistically expected from [rare disease] PROMs," according to a 2021 study.[64] In addition, the aforementioned heterogeneity of rare disease makes it challenging to capture consequential outcomes that can be accurately generalized to the entire patient population.[65] These challenges often preclude the creation of rare disease PROMs, forcing trials for rare

disease therapies to rely on less specific, disease-agnostic PROMs.

By having few PROMs in rare disease, researchers may not be fully capturing the treatment experience of diverse patient populations. For example, racial and ethnic minorities report lower satisfaction with the quality of care they receive as well as difficulty in accessing care.[66] PROMs could be a useful tool in measuring the extent of the disparity, but, for patients with rare diseases, these disparities may not be captured due to a lack of PROMS. More broadly, it may be difficult for HTAs that rely on PROMs to develop an accurate, comprehensive understanding of an orphan drug's benefits and value when performing evaluations.

Value-Based price evaluation might not be meaningful when applied to rare conditions.

Orphan drugs provide vast benefits for patients, many of whom either have no or very few treatment options for their symptoms. However, the metric that HTAs most commonly use in measuring a drug's value, QALYs, fails to account for a variety of these benefits, causing orphan drugs to remain undervalued.[67] QALYs are a measurement of "how well all different kinds of medical treatments lengthen and/or improve patients' lives," year by year, according to the Institute for Clinical and Economic Review (ICER).[68,69] Most HTA bodies calculate a drug's contributing QALYs and compare the sum to the drug's cost. If a drug contributes few QALYs but is high cost, it may be low value for money— making the drug less likely to be referred for reimbursement. In many European countries, private and public payers typically consider these QALY-reliant reimbursement decisions when determining whether they will cover a new treatment.[70]

However, rare disease experts and advocates state that QALYs are ill-suited for measuring the value of orphan drugs.[71] For one, HTA bodies compare the QALYs of a new therapy to the QALYs of the existing standard of care for a particular condition.[72] The new therapy is then assigned a QALY value based on the QALYs gained compared to the standard of care.[73] Identifying a standard of care for rare diseases, however, may be a challenge in practice. First, in many cases, there are no available treatments for many rare diseases [74], resulting in no comparators for the new treatment option. While "no treatment" could be considered a valid comparator from an HTA perspective, in practice, clinicians may consider no treatment to be unethical if a new, efficacious treatment comes to market.[75] Second, even if some treatments are currently available, determining what the typical standard of care is may be a challenge due to the limited real-world data available for diseases that afflict so few patients.[76]

Another challenge in using QALYs is that health gains are treated the same for all people regardless of disease severity. Recent studies have shown that individuals place a higher value on health improvement for patients with more severe diseases. One study on willingness to pay found that most people were willing to spend more money on a QALY gain for people with severe disease compared to more moderate illnesses.[77] Cost-effectiveness analyses value all incremental QALY improvements equally, rendering them blind to contextual factors such as disease severity, expected lifespan, the current availability of alternative treatments, and the likelihood that other treatments will be developed in the future. Consequently, a treatment for a common, mild disease with greater incremental QALY gains than a treatment for a rare, severe disease could be deemed the more valuable of the two, even though the latter might treat symptoms of a disease that has few to no treatment alternatives.[78] New orphan drugs are often deemed as providing fewer QALYs for their cost point, resulting in more negative reimbursement decisions and lower patient access.

As stated by the National Council on Disability, QALYs "[reduce] the value of treatments that do not bring a person back to 'perfect health,'" something that is not always possible for patients with rare diseases.[79] For patients with rare and often untreatable conditions, the day-to-day "quality" of their lives is subjective and more difficult to measure. For some patients, reaching a milestone like sitting up by themselves or walking with assistance might have a huge impact on their quality of life, but these nuances might not be considered. Similarly, a life-extension of a few

years might be significant for a rare disease patient who has a shorter life expectancy to begin with and no treatment options. However, these QALYs are still counted the same as someone with a common illness who might experience a greater life-extension due to greater progress in research and development.

Furthermore, QALYs only measure benefits provided to patients, neglecting to consider a drug's potential impact on caregivers and society as a whole. Orphan drugs can have tremendous benefits for caregivers, lifting some of the significant financial and emotional burdens they carry. For example, 34 percent of caregivers for patients with cystic fibrosis (CF)—a disease that severely damages the lungs and digestive system— suffer from clinical depression.[80] They are also more prone to higher job turnover and a higher probability of giving up their desired career.[81] Caregiver burden contributes to the overall disease cost, offering an additional financial benefit that QALYs neglect to account for; the cost of caregiving can account for as much as 31 percent of the total cost of one's disease.[82] New treatments that could improve rare diseases that result in immobility or loss of motor function—like multiple sclerosis (MS)— would have tremendous benefit for caregivers, but HTAs rarely measure or consider these benefits explicitly.

> *"In their current form, QALYs do not consider the holistic impact of orphan drugs, failing to incorporate many of the life-altering benefits that they bring."*

In their current form, QALYs do not consider the holistic impact of orphan drugs, failing to incorporate many of the life-altering benefits that they bring. This, coupled with higher drug costs for orphan drugs make HTA bodies more likely to deem orphan drugs unworthy of their price. This ultimately prevents orphan drugs from coming to market, or at least being reimbursed at a sufficient level to ensure patient access, leaving patients affected by those conditions with minimal treatment options.

Health Equity

While the prevalence and impact of rare disease may vary across races and ethnicities due to a combination of genetics, socioeconomic factors, and systemic racism, the burden of rare disease in patients of color is further compounded by inequities in the U.S. health care system. Health disparities, including lower access to care and a higher prevalence of chronic health conditions among people of color, create a large racial gap in health outcomes in the U.S.[83] These challenges underscore the importance of ensuring equitable access to innovations in rare disease therapies. However, HTA bodies' evaluation methodologies may fail to recognize the value of a treatment to specific patient populations, inhibiting access to care for vulnerable populations.

HTA bodies limit their value assessment to QALYs, ignoring new treatment benefits[84] that impact patients' lives more holistically and undervaluing new treatments in ways that may disproportionately affect racial and ethnic minority populations.[85] QALYs, which ICER relies on heavily in assessing the value of orphan drugs, do not account for a treatment's non-health related benefits—such as ability to return to work or school—or indirect costs, including caregiving expenses, mental health challenges, and loss of productivity.[86] These benefits typically have a disproportionate impact on racial and ethnic minorities who are more likely to be low-income and to struggle with food and housing insecurity, factors that contribute directly to health outcomes.[87] As a result, by failing to consider a treatment's non-health related benefits or the ways a treatment may reduce indirect costs, ICER may undervalue orphan drugs that may be particularly impactful for vulnerable patient populations.

HTAs' narrow definitions of value may also underestimate the benefits of eliminating the negative side effects of existing treatment alternatives, some of which disproportionately affect racial and ethnic minority patients. For example, advocates argue that ICER's assessment of new myasthenia gravis treatments did not fully capture

the impact of the side effects of corticosteroids—a pre-existing, commonly-used treatment for the disease—which is a regrettable oversight given that "side effects can contribute as much to patient disability as the disease itself," according to patient reports.[88] Furthermore, the long-term use of corticosteroids contributes to the progression of serious health conditions to which Black people are already predisposed, such as diabetes and hypertension.[89] New drugs that eliminate these side effects have the potential to improve both quality of life and health outcomes – particularly in Black patients. By undervaluing the benefits accrued to these patients and limiting or denying access to alternative treatments, however, the HTA value assessment framework may inadvertently perpetuate health disparities.

HTA IN THE U.S. COULD LIMIT ACCESS TO ORPHAN DRUGS

As policymakers consider the merits of establishing a national HTA body in the U.S., the potential impact on access to orphan drugs must be a key consideration. Currently, there are a number of non-governmental organizations that perform HTA functions including ICER and the Innovation and Value Initiative (IVI).[90] ICER is a non-profit, independent organization that performs evaluations and releases reports on the value of medicines in an effort to align the drug's price with how well the medicine improves the lives of patients. The organization's value assessment uses clinical and economic evidence to determine a value-based price for each drug based on QALYs to determine whether the treatment improves or lengthens patients' lives.[91] ICER's value-based price is then compared to the drug's list price.

In an attempt to accommodate the unique challenges of assessing rare disease, ICER made modifications to its framework for assessing the value of new treatments for "ultra-rare disease" in 2017. However, it does not include special dispensations for other rare diseases and still evaluates the cost-effectiveness of orphan drugs using roughly the same metrics that it uses for other treatments.[92]

"ICER's evaluation framework does not consider all of the benefits that orphan drugs bring, resulting in evaluations that are less likely to deem orphan drugs cost-effective."

As a result, ICER's evaluation framework does not consider all of the benefits that orphan drugs bring, resulting in evaluations that are less likely to deem orphan drugs cost-effective. Given that some payers, both public and private, heed ICER's guidance in determining whether to include a new drug in their formulary, ICER's lack of a proper rare disease-specific evaluation framework has the potential to restrict access to orphan drugs for patients with rare diseases in the U.S.[93] Ultimately, due to the challenge of setting a specific willingness to pay threshold for rare diseases—or the maximum amount ICER is willing to pay for a particular orphan drug— ICER passes orphan drug reimbursement decisions to payers.

"A national HTA body, operating with the power and authority of the U.S. government, could yield even more power over payers' reimbursement decisions concerning orphan drugs, with potentially devastating consequences for the rare disease community."

ICER's influence on payer decisions is significant and grows stronger every year. In 2016, 49 percent of payers reported that ICER recommendations influenced their formulary decisions; in 2018, that number rose to 78 percent.[94] A national HTA body, operating with the power and authority of the U.S. government, could yield even more power over payers' reimbursement decisions concerning orphan drugs, with potentially devastating consequences for the rare disease community.

RARE DISEASE REIMBURSEMENT GLOBAL LANDSCAPE

While European HTA bodies offer an alternative to ICER, applying standard European HTA practices to orphan drugs could delay or prevent rare disease therapies from coming to market. Standard HTA often utilizes a cost-per-QALY threshold to set prices. However, given that QALYs do not accurately measure the full value of orphan drugs, standard HTA's reliance on QALYs often results in the undervaluation of orphan drugs, reducing patient access. In part due to their usage of QALYs, general HTA processes do not successfully assess the value of orphan drugs.

To overcome this challenge, many countries with HTA bodies offer orphan drugs special considerations in some steps of the assessment process.[95]

"Many countries with HTA bodies offer orphan drugs special considerations in some steps of the assessment process... However, these accommodations are often insufficient to overcome the challenges of a traditional HTA framework for orphan drugs."

These special considerations vary by country, but four common examples are: assumed benefit thresholds based on budget impact limits; application of standard value assessment with higher willingness to pay thresholds; specialized review pathways; and pre-authorization programs. However, these accommodations are often insufficient to overcome the challenges of a traditional HTA framework for orphan drugs.

ASSUMED BENEFIT THRESHOLDS ARE UNDERMINED BY NEW LEGISLATION AND RIGID EVIDENCE REQUIREMENTS

Recognizing the barriers to assessing orphan drugs, some European HTA bodies such as France and Germany allow orphan drugs that are already deemed safe and effective to bypass some of the HTA process by granting them an automatic, assumed benefit compared to existing treatments if: i) the treatment is approved by the EMA and ii) the total budget impact is below a specific threshold. With an automatic, assumed benefit, approved orphan drugs are automatically deemed beneficial to patients, meaning that HTA bodies cannot issue a negative reimbursement decision – a decision in which the HTA body does not recommend reimbursement for any population.[96] However, to receive these benefits in most countries, orphan drugs must remain below a certain price—called an assumed benefit threshold—meaning more expensive medicines are excluded. In Germany, manufacturers of new pharmaceuticals are required to submit clinical evidence demonstrating their drug's benefit.[97] The Federal Joint Committee (G-BA) – the ultimate decision-making HTA body in Germany – uses this clinical evidence to evaluate the new drug's additional benefit relative to a comparator to determine if the new drug provides substantial new benefits compared to the existing therapy.[98] For many or even most rare diseases, few treatments exist, which typically means there are few to no comparators for orphan drugs undergoing HTA, let alone substantial clinical evidence for those comparators. As a result, orphan drugs that cost the state-run health care system less than €50 million annually are granted an automatic, assumed benefit.[99,100] By receiving an automatic, assumed benefit, orphan drugs do not have to be assessed against a comparator, seemingly addressing certain barriers to market entry. Due in part to the assumed benefit threshold, G-BA boasted a 98 percent approval rating for orphan drugs, the highest approval rating of all countries included in a July 2020 study.[101]

Similarly, the Haute Autorité de Santé (HAS) Transparency Committee (TC), France's HTA body, applies an automatic, assumed benefit if a market-authorized orphan drug's total budget indication is less than €30 million per year.[102] The HAS TC approved 92 percent of orphan drugs between 2013 and 2019, the second highest approval rating of countries evaluated in a July 2020 study.[103]

While a relatively high percentage of orphan drugs receive reimbursements in these countries, significant barriers to access and innovation persist. Because orphan drugs are not required to undergo evaluation against a comparator in Germany, most orphan drugs (55 percent) receive a non-quantifiable benefit rating—the absolute lowest recommendation an orphan drug can receive in the German system.[104] In addition, orphan drugs that cost more than the assumed benefit threshold (€50 million over a 12-month period) receive no protection from standard HTA practices and no automatic, assumed benefit. These orphan drugs are then required to undergo the same evaluation as non-orphan drugs, including re-assessment with an appropriate comparator.[105] If no appropriate comparator is available, an improvement in benefit cannot be proven.[106]

Recent reforms may further undermine the assumed benefit threshold. In 2019, Germany passed the *Gesetz für mehr Sicherheit in der Arzneimittelversorgung* (GSAV), legislation that added inpatient care and prescriptions to the drug's overall budget impact, increasing the likelihood that a new drug will reach the €50 million automatic benefit threshold.[107] Incorporating a broader range of costs means that fewer orphan drugs will receive the automatic, assumed benefit. In France, low reimbursement rates from public funds undermine the advantage of an automatic benefit threshold for orphan drugs. Some academics argue that reimbursement from public funds is necessary to ensure orphan drugs are truly accessible to patients on the market as many patients rely on public reimbursement to help absorb orphan drugs' higher price tags.[108] However, about 69 percent of France's orphan drugs were reimbursed using public funds, leaving the country behind Germany (90.8 percent) and England (70.6 percent), but above the EU average of 65 percent.[109]

Evidence suggests that automatically granting orphan drugs an additional benefit may simply ameliorate market entry for new orphan drugs with non-quantifiable benefits rather than addressing the root issue at hand: HTA systems that lack orphan disease-specific frameworks do not adequately evaluate orphan drugs' value when determining pricing and reimbursement.

OVERLY RESTRICTIVE DRUG PRICE ADJUSTMENT THRESHOLDS MAY LIMIT PATIENT ACCESS TO RARE DISEASE THERAPIES

To rein in costs, some countries adjust a drug's price based on its perceived value. To determine this value, the Japanese HTA system uses incremental cost-effectiveness ratios (ICERs)—the difference in cost between the new treatment and that of a comparator, divided by the difference in benefit relative to a comparator[110] — as evidence of the cost-effectiveness of new health technologies.[111] If a drug's ICER is below a certain cost per QALY—considered the drug price adjustment threshold—the drug provides enough value to warrant its price.[112] However, if a non-orphan drug's ICER is above that cost, the price is adjusted incrementally. For non-orphan drugs in Japan, the drug price adjustment threshold begins at ¥5 million per QALY.

Recognizing that orphan drugs are not properly valued using QALYs, Chuikyo, one of Japan's HTA bodies, instituted price thresholds for orphan drugs that are 1.5 times higher (¥7.5 million per QALY) than the threshold for non-orphan drugs.[113] Chuikyo hoped the policy would ensure that orphan drug makers were not punished for developing pharmaceuticals that appeal to smaller markets. However, the policy also sets a price cap for orphan drugs, determining that any pharmaceuticals that cost more than

¥15 million per QALY are adjusted to a standard maximum rate.

Setting a maximum reimbursement level for orphan drugs would greatly deter investment in research and development for rare diseases.

Although the increased price adjustment thresholds are meant to account for orphan drugs' unique value, the Japanese HTA system's reliance on QALYs could restrict the number of orphan drugs that come to market.[114] In addition, the use of price thresholds in any capacity creates a disincentive for rare disease research by cutting into manufacturers' return on investment.[115] By setting a maximum cost cap for orphan drugs, some expensive orphan drugs might be priced significantly below their value, potentially deterring investment in orphan therapies that could benefit patients across the country.[116]

HTA FRAMEWORKS TAILORED TO RARE DISEASE DRUGS ARE UNDER UTILIZED

Recognizing that the traditional HTA structure fails to properly assess the value of orphan drugs, some countries employ a bespoke assessment framework for orphan drugs. In England, the National Institute for Health and Care Excellence (NICE) – the national HTA body – offers a discrete evaluation pathway for rare disease drugs called the Highly Specialized Technologies (HST) pathway. The HST pathway offers a more favorable, flexible approach to evaluating orphan drugs[117] by increasing the maximum amount that the UK's National Health Service (NHS) would be willing to pay for a given drug, referred to as the willingness to pay threshold. The HST pathway also grants orphan drug makers the freedom to decide what form of health economic evaluation they submit,[118] and to submit additional information they believe the appraisal committee should consider to strengthen the case for high reimbursement, such as the nature of the condition treated and the drug's impact beyond easily measurable health benefits. Both of these exceptions empower drug makers to make up for a lack of clinical data.[119] As of January 2021, 100 percent of orphan drugs evaluated through HST received positive recommendations since the program's inception.[120]

Although the HST pathway would appear to be an effective means of improving access to orphan drugs, in practice access to orphan drugs in England is highly restricted. While the HST pathway is better adapted to conducting value assessment of orphan drugs than the standard NICE approach, most orphan drugs in England do not qualify for the HST pathway, instead falling under Single Technology Appraisal (STA) purview. STA, England's traditional HTA framework for non-orphan drugs, does not implement the higher willingness to pay or broader value criteria employed under HST.[121] Due to the strict criteria for HST, its impact on orphan drug access is minimal. For instance, while NICE established the HST pathway back in 2013, it only finalized 12 HST assessments as of January 2021.[122]

Orphan drugs evaluated through STA face longer reimbursement times and lower recommendation rates in England compared to most other European countries. NICE has the most restricted orphan drug reimbursement decisions in Europe, with only 68 percent receiving reimbursement.[123] A 2019 study found that England issued negative reimbursement recommendations for 10.9 percent of orphan drugs, compared to 8.2 percent in Germany, 4.6 percent in France, and 1.9 percent in Spain.[124] Furthermore, NICE's reliance on STA to evaluate pharmaceuticals that should be evaluated through HST makes the assessment of orphan drugs inefficient. Studies indicate that it takes NICE longer to evaluate orphan drugs (370 days on average) compared to non-orphan drugs (277 days on average).[125] NICE demonstrates that the establishment of a rare disease-specific HTA framework is not enough—it must also be widely deployed to be effective.

STRICT CRITERIA DIMINISH THE BENEFITS OF PRE-AUTHORIZATION PROGRAMS

Some countries—including Italy and France—have pre-authorization programs, which allow certain orphan drugs to receive reimbursement decisions prior to authorization by the European Commission (EC).[126] The aim of these programs is to help some pharmaceuticals—particularly those for rare diseases with no current treatment alternatives—to avoid delayed reimbursement decision times. However, strict criteria for these programs can greatly limit the number of orphan drugs that benefit from the pathways. In Italy, Law 648 of 1996 allows early market access on a national level for innovative medicines – including orphan drugs – for which there is no alternative therapy available and for some off-label uses.[127] In order to qualify for pre-authorization, innovative pharmaceuticals in Italy must be authorized in another European country, be undergoing clinical trials, or currently be used to treat a different condition in the country.[128] In addition, the drug must prove that its benefit outweighs its risk through a Phase II study. Experts maintain that the pre-authorization program helps orphan drugs that fall under the "innovative medicine" umbrella circumvent long reimbursement times.[129] Italy has one of the shortest times from authorization to reimbursement at 18.6 months, compared to 19.5 months in France.[130]

However, the criteria for these pre-authorization programs are often strict, meaning many orphan drugs may not qualify for pre-authorization. For instance, according to the Italian Medicines Agency, in Italy an orphan drug that is not the first drug to treat a certain condition must demonstrate that its indication is "compliant with research conducted within the national and international medical-scientific community, according to parameters of cost-effectiveness and appropriateness,"[131] making it subject to cost-effectiveness considerations that often prevent orphan drugs – which are inherently more expensive —from coming to market. In addition, Italy does not have a special reimbursement or pricing process for orphan medicines that are already licensed.[132] Instead, they are evaluated through a standard HTA and reimbursement process that considers budget impact and cost-effectiveness and is not designed to accommodate orphan drugs.[133]

Evidence suggests that a lack of specialized HTA for orphan drugs might result in the Italian HTA body recommending low reimbursement rates for orphan drugs, likely because the medicines were not found to be cost-effective under a traditional HTA assessment structure. According to a May 2019 study, Italy's national system only reimburses 59 percent of orphan drugs authorized by the EC.[134] Without public funding, drug makers could be forced to set their prices excessively low, causing them to lose money on their investment and potentially disincentivizing further innovation. On the other hand, rare disease patients could be forced to pay prices that are unaffordable without government assistance.

CASE STUDIES

While most countries that employ HTA bodies adopt exceptions to the standard value assessment process when evaluating orphan drugs, in practice, access to orphan drugs remains limited in countries with centralized HTA bodies.[135] To better understand how HTA policies have impacted treatment access for patients with rare disease, we evaluate three rare disease case studies: ORKAMBI® for treating cystic fibrosis, OCREVUS® for treatment of patients with a rare form of multiple sclerosis, and SPINRAZA® for the treatment of spinal muscular atrophy. In all three cases, HTA processes limited patient access to new, breakthrough treatments that could have improved health outcomes of patients in dire need. Each of these case studies is discussed below.

Case Study #1: Cost Concerns Deny Thousands of Patients Access to Needed Treatment

Ivacaftor/lumacaftor – sold under the brand name ORKAMBI®– was developed to treat cystic fibrosis, an inherited condition that causes people to produce mucus that is thicker and stickier compared to people without the condition, leading to clogged and damaged critical organs.[136] Cystic fibrosis is a rare, genetic disease that affects approximately 100,000 people around the world, including about 10,600 people in the UK.[137] To improve the lives of people living with cystic fibrosis, U.S.-based Vertex pharmaceuticals developed Orkambi, which works by targeting the chloride channels in the body that control mucus production. Orkambi is specifically effective for patients that have the F508del mutation on both copies of the gene, the most common mutation in people living with cystic fibrosis.[138]

Orkambi was found to reduce hospitalizations among cystic fibrosis patients, and when the drug was submitted for consideration to NICE in 2015, the agency concluded that the drug could have clinical benefits for about 2,750 cystic fibrosis patients in England. However, like many orphan drugs in the UK, Orkambi was not eligible for the HST pathway, instead undergoing assessment through the STA pathway which is not designed to evaluate orphan drugs. In 2016, NICE denied government reimbursement for the drug, saying that the cost of the drug was too high to be a "cost-effective use of NHS resources." In its assessment, the HTA body further determined that Orkambi, which would cost about £104,000 per patient, showed "modest" benefits compared to existing treatments.[139] In the NICE announcement, the agency said it would "only recommend treatments when [they] are certain they are both clinically effective and represent good value for money," saying they would "welcome" Orkambi "at a cost-effective price."[140]

The debate over the cost-effectiveness of the drug continued for more than three years. Meanwhile in comparable countries, including the U.S. and other parts of Europe, Orkambi had been available as a treatment since 2015. As the wait continued, Orkambi proved to reduce rates of lung function decline by nearly 50 percent in cystic fibrosis patients. The Cystic Fibrosis Trust further suggested that additional real-world data demonstrating the long-term benefits of Orkambi could be collected and distributed to the HTA body to speed up the decision; however, NICE officials said they would only review the data if the price were lowered.[141] In 2018, after meeting with the Cystic Fibrosis Trust over the decision, Sarah Wollaston, MD, who then served as Member of Parliament and Chair of the Health and Social Chair Committee, wrote a letter to Jeremy Hunt, Member of Parliament and Secretary of State for Health and Social Care, regarding the drug's denial. Dr. Wollaston's letter attached a briefing which noted that because Orkambi was not eligible as an HST, "[t]his meant Orkambi was appraised using the same rules as a treatment with a much larger patient population. As a result, Orkambi was considered nowhere near cost-effective. To meet the requirements of an STA, Orkambi would need to be over five times cheaper."[142]

After years of pressure from cystic fibrosis advocates and patients, in 2019, the NHS reached a deal with Vertex where it agreed to appraise Orkambi and other cystic fibrosis pharmaceuticals if the company submitted its full portfolio for appraisal.

"The decision [to appraise Orkambi in the UK] came years after the drug was made available in other countries, and activists maintained that the HTA body's fixation on cost— and its disregard of additional proven benefits—led to unnecessary suffering and deaths among cystic fibrosis patients."

The appraisal is slated to conclude in 2021 and will include an 18-month period of real-world data collection.[143] However, the decision came years after the drug was made available in other countries, and activists maintained that the HTA body's fixation on cost—and its disregard of additional proven benefits—led to unnecessary suffering and deaths among cystic fibrosis patients.

Case Study #2: Strict Early Access Criteria Prevent Multiple Sclerosis Patients from Accessing First-Of-Its Kind Innovation

Ocrelizumab, sold as OCREVUS®, is the first monoclonal antibody treatment approved to treat primary progressive multiple sclerosis (PPMS), a rare form of multiple sclerosis (MS)—a disease of the central nervous system. PPMS, unlike other forms of MS, is a condition that progressively worsens due to damaged and lost nerves.[144] People afflicted with the condition experience disability in their limbs and decreased mobility over time, which greatly impacts their quality of life.[145] While there are a number of medications indicated for relapse remitting multiple sclerosis (RRMS), ocrelizumab was the first treatment approved specifically for patients with PPMS. While about a quarter of PPMS patients reach a disability milestone after five years, patients treated with Ocrevus were less likely to reach these milestones. Patients treated with Ocrevus are 24 percent less likely to experience disease progression than those who do not receive treatment.[146]

Ocrevus was approved by the FDA in 2017 and by the EU in 2018 for treatment of PPMS and RRMS. The drug also showed positive Phase III efficacy results, which were further reinforced by exploratory analyses.[147] However, the drug was made available sooner through France's early access program. Shortly after, an opinion issued by the French HTA body HAS determined the drug yielded no additional benefit compared to a placebo. The drug was taken off the market for patients who were newly eligible, stating the results of the opinion were incompatible with the criteria of the early access program.[148] In comparison, NICE, which does not have an early access program, performed an appraisal with a pricing agreement, and the drug was recommended.[149] In this case, the strict criteria of the early access program—which is often used for innovative treatments like orphan drugs—only delayed access to a groundbreaking treatment for more than 49,000[150] MS patients in France.

Case Study #3: Subset of Patients Miss Out on Breakthrough Therapy Due to Strict HTA Eligibility

SPINRAZA® (nusinersen), developed by American biotechnology company Biogen, is the company's first-in-class treatment for spinal muscular atrophy (SMA), a genetic rare disease that affects the central and peripheral nervous system, as well as voluntary muscle movement.[151] People with spinal muscular atrophy experience severe muscle weakness and waste making the disease fatal for many children diagnosed with the condition. In fact, about 68 percent of children with spinal muscular atrophy type 1—the most common form of the disease—die before they turn two years old.[152]

In multiple clinical studies of more than 170 patients, Spinraza was shown to improve motor function in patients with infantile-onset spinal muscular atrophy compared to patients in the control group. For instance, a larger percentage of patients (51 percent versus 0 percent) treated with the drug were able to reach motor milestones including standing, walking, and sitting unassisted at ages when those functions are expected to be impossible.[153] Spinraza also reduced patients' chance of death or permanent ventilation by 47 percent[154] compared to patients in the control group.[155]

In 2016, the FDA approved the drug for spinal muscular atrophy and it was later given marketing authorization by the European Commission in 2017. However, despite Scotland and other parts of Europe granting approval to the drug, Spinraza experienced approval delays in England after NICE rejected its proposed price in August 2018, leaving patients in the UK without access to the only available treatment for the devastating, fatal disease.[156] Spinraza, like many other rare disease drugs, did not qualify for NICE's HST appraisal pathway used for orphan and ultra-orphan drugs, and was instead forced to undergo consideration under NICE's standard STA process.[157] Through STA, NICE found that the drug's cost, which was about £450,000 for the first year of treatment and £225,000 for subsequent years, was too high to justify the treatment gains, despite the drug showing a "substantial benefit."[158] In a statement, NICE claimed that it had "significant uncertainties, particularly around [the drug's] long-term benefits,"[159] despite new data introduced that year that showed infants, teens, and adults exhibited continued improvement on the drug.[160]

Similar to the case with Orkambi®, activists pushed for NICE to reconsider its decision, especially as new data continued to show the drug's effectiveness. Finally, in 2019, NICE formed a managed access agreement (MAA) with the NHS and Biogen, which allowed Spinraza to be available to a subset of patients as long as NICE could continue to collect data on the treatment's efficacy and financial impact. However, even the MAA was limited – Spinraza was available to almost all spinal muscular atrophy patients except for those with type 3 who lost their ability to walk. In May 2021, NICE announced that "the review has concluded that it is appropriate to extend the clinical eligibility criteria to allow access to [Spinraza] for type III spinal muscular atrophy patients who aren't able to walk,"[161] making the one-of-a kind treatment available to all. However, it is unknown how many more patients may have benefited from the treatment had it been available in 2018.

Overall, the strict criteria for the HST appraisal pathway has limited many orphan drugs from being widely available. Of the 24 STA reviews of orphan drugs conducted by NICE between 2013 and 2017, only 13 percent were recommended for the full population that was made eligible through EC authorization compared to full recommendation for 66 percent of non-orphan medicines.[162]

DISCUSSION

Since the enactment of the *Orphan Drug Act* in 1983, orphan drug research and development has undergone its largest period of growth in history. In fact, over 5,000 drugs and biologics have been granted orphan drug designation in the decades following ODA's passage.[163] These discoveries have ameliorated both the lifespan and quality of life of myriad patients with rare diseases.

Groundbreaking discoveries in rare disease treatment come at a significant cost—pharmaceutical companies must set prices that are high enough to cover research and development costs[164] despite small patient populations. As a result, a 2015 report found that the average cost of an orphan drug in the U.S. was $111,820 in 2014, compared to $23,331 for treatments for more common diseases.[165] Furthermore, payers are increasingly electing to pass the cost of treatment onto patients, leaving them with high out-of-pocket costs.

While some policymakers have called for the use of a centralized HTA body to contain costs, doing so is problematic along a number of dimensions:

- **Clinical evidence from rare disease trials may be less precise than evidence found through trials for non-rare diseases, which can utilize a broader range of study designs.** To overcome inherently small patient populations, rare disease clinical trials must employ methods such as non-randomized study designs and single-arm studies, which do not use a control group, potentially causing HTA bodies to question the validity of clinical trial results.[166]

- **The use of QALYs—which fail to measure many of the life-altering benefits of orphan drugs—and cost-effectiveness thresholds can cause HTA bodies to deem orphan drugs unworthy of their price**—restricting reimbursement rates as well as the number of orphan drugs that come to market. In addition, the use of price thresholds in any capacity creates a disincentive for rare disease research by resulting in reimbursement levels that are too low to cover the cost of pharmaceutical development, ultimately cutting into manufacturers' return on investment.

- **When HTA bodies conduct their economic evaluations, they typically do not consider that society places a higher value on treatments for more severe diseases.**

- **HTA bodies do not consider indirect costs or non-health related benefits—such as relieved caregiver burden, improved mental health, and return to work— which can disproportionately impact underserved and underrepresented communities.** By failing to consider these benefits, HTA bodies may undervalue orphan drugs that are particularly beneficial for racial and ethnic minority patients or other vulnerable patient populations, inadvertently perpetuating existing health disparities.

Although some countries have created special exceptions for orphan drugs in the value assessment process, other HTA policies caused these exceptions to fall short of their intent. England's NICE, for example, offers the HST assessment pathway for orphan drugs, which is more flexible than the standard HTA pathway for non-orphan pharmaceuticals.[167] However, the HST pathway's strict eligibility requirements preclude most orphan drugs from being assessed through the pathway.[168] Instead, most orphan drugs are evaluated under STA, which does not grant orphan drugs special considerations. These strict HST eligibility criteria led NICE to deny government reimbursement for a cystic fibrosis treatment that reduced hospitalizations, preventing thousands of cystic fibrosis patients in England from accessing the drug's proven clinical benefits.[169] Of the 24 STA reviews of orphan drugs conducted by NICE between 2013 and 2017, only 13 percent were recommended for the full population made eligible through EC authorization.[170]

In Italy, policymakers elected to grant orphan drugs a policy exception rather than creating a specialized pathway.[171] The country instead offers a pre-authorization program to allow orphan drugs earlier market access.[172] However, strict eligibility criteria for the pre-authorization program preclude most orphan drugs from participating.[173] Worldwide, regardless of HTA bodies' attempts to grant orphan drugs special exceptions or frameworks, access to orphan drugs remains limited.

Despite its shortcomings, the U.S. health care system has served as a remarkable laboratory for innovation in rare disease treatments that benefits patients around the world. Introducing a national HTA in the U.S. has the potential to thwart progress at a time when 95 percent of rare diseases still have no approved treatment.[174] Policymakers must consider the experience of rare disease patients in countries that have adopted such systems, where orphan drugs often face insurmountable challenges in value assessment and market access. As a global leader in rare disease innovation, the ramifications of implementing standard HTA in the U.S. could be far-reaching and long-lasting for patients seeking access to life-saving orphan drugs.

KEY TERMS/GLOSSARY

- **Assumed benefit:** Designation granted by an HTA body to a new treatment that signals that the treatment offers a new benefit for patients relative to existing treatments. In some countries, orphan drugs are granted an assumed benefit because there are no treatment alternatives, meaning that the new treatment will provide some degree of benefit to patients.
- **Assumed benefit threshold:** Cost threshold for orphan drugs that allows approved orphan drugs priced below a certain level to be automatically deemed beneficial to patients—meaning that HTA bodies cannot issue a negative reimbursement decision.
- **Authorization:** Approval to market a medicine in a given country.[175]
- **Cost-effectiveness analysis:** Comparison of how a new treatment impacts treatment cost, health benefits (e.g., reduced mortality or morbidity), and health risks relative to the previous standard of care.[176]
- **Health Technology Assessment (HTA):** Multidisciplinary process that measures the medical, ethical, economic, and social impact of a new health technology to determine its value. The purpose of HTA is to inform decision-making regarding drug reimbursement and/or drug pricing.
- **Highly specialized technologies pathway (HST):** Specialized evaluation pathway for orphan drugs established by NICE, the English HTA body, designed to grant orphan drugs special exceptions in the HTA process, increasing their probability of receiving a positive reimbursement decision.
- **HTA body:** Public or private organization that conducts HTA (e.g., NICE or ICER).
- **Incremental cost effectiveness ratio (ICER):** Difference in cost between a new treatment and that of a comparator, divided by the difference in benefit relative to a comparator.[177]
- **Innovative medicine:** Medicine that has never previously received authorization.[178]
- **Institute for Clinical and Economic Review (ICER):** Non-profit, independent organization in the U.S. that performs evaluations and releases reports on the value of medicines in an effort to align the drug's price with how well the medicine improves the lives of patients.
- **Managed Access Agreement (MAA):** Agreements between the NHS in England and pharmaceutical companies to authorize a drug to become available for a limited period of time at a discounted price.[179]

- **Negative reimbursement decision:** Decision in which an HTA body does not recommend a treatment for reimbursement for use by any population.
- **Non-randomized trial:** Clinical trial in which study participants are not arbitrarily assigned to various treatment groups.[180]
- **Orphan drug:** Pharmaceutical treatment designed to prevent, diagnose, or treat a rare disease.[181]
- **Patient reported outcome measures (PROMs):** Self-reported measurements of a patient's experience with their disease and treatment. Used to convey a more comprehensive understanding of a treatment's impact beyond direct clinical results.
- **Pre-authorization programs:** Programs that allow certain orphan drugs to receive reimbursement decisions prior to market authorization.
- **Positive reimbursement decision:** Decision in which an HTA body recommends a treatment for reimbursement for use by a specific population.
- **Quality-adjusted life years (QALYs):** Metric used to quantify how much certain medical treatments change patient morbidity (i.e., quality of life) and mortality (i.e., survival).[182]
- **Randomized control trial (RCT):** Study design commonly viewed as the gold standard in which patients are randomly assigned to either a group receiving the treatment or a control group.
- **Rare disease:** Disease that affects fewer than 200,000 patients in the U.S.[183]
- **Reimbursement:** Amount that a payer agrees to spend on a treatment.[184]
- **Single arm studies:** Study design in which all participants receive the treatment.
- **Single Technology Appraisal (STA):** NICE's traditional HTA framework for non-orphan drugs as well as orphan drugs that do not meet the criteria for HST consideration.
- **Standard of care:** Commonly agreed-upon diagnosis and treatment process that physicians should abide by for a particular kind of patient, disease, or clinical situation.[185]
- **Surrogate endpoints:** Outcome of a clinical trial researchers measure to determine the effectiveness of a new treatment. Surrogate outcomes are not the true outcome researchers are hoping the treatment will create, such as prolonged lifespan or quality of life, but are easier-to-measure outcomes that can reasonably serve as a surrogate for outcomes that are more difficult to measure in a timely fashion.
- **Value assessment:** Process through which HTA bodies assess a new treatment's value, considering a wide variety of clinical and economic evidence, to determine the drug's rightful price.
- **Willingness to pay threshold:** Maximum amount a payer is willing to spend on a particular treatment.[186]

Endnotes

1 Nestler-Parr, Sandra, Daria Korchagina, Mondher Toumi, Chris L. Pashos, Christopher Blanchette, Elizabeth Molsen, Thomas Morel, et al. "Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group." Value in Health. Elsevier, May 2018. https://www.sciencedirect.com/science/article/pii/S1098301518302742.

2 Ibid.

3 Rand, Leah, and Aaron Kesselheim. "Controversy over Using Quality-Adjusted Life-Years in Cost-Effectiveness Analyses: A Systematic Literature Review." Health Affairs, September 2021. https://www.healthaffairs.org/doi/10.1377/hlthaff.2021.00343.

4 Zamora, Bernarda, Francois Maignen, Phill O'Neill, Jorge Mestre-Ferrandiz, and Martina Garau. "Comparing access to orphan medicinal products in Europe." Orphanet Journal of Rare Diseases. BioMed Central, May 3, 2019. https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1078-5.

5 "Quality-Adjusted Life Years and the Devaluation of Life with Disability." National Council on Disability, November 6, 2019. https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf, p. 11.

6 Tchebaniouk, Elizaveta. "Japan Incorporates Cost-Effectiveness Into Its HTA: What Manufacturers Can Do to Prepare." Windrose Consulting Group, n.d. https://windrosecg.com/news-events/2021/7/1/japan-incorporates-cost-effectiveness-into-its-hta-what-manufacturers-can-do-to-prepare.

7 Zhou FF, Ward K, Kennedy A, Roberts TS, Gaebler JA. Value for Whom?: Incorporating Patient Perspectives into Value Assessment for Novel Cell and Gene Therapies. Health Advances. 2020. http://www.pipcpatients.org/uploads/1/2/9/0/12902828/cgt_therapies_webinar_draft_final.pdf.

8 "Quality-Adjusted Life Years and the Devaluation of Life with Disability." National Council on Disability, November 6, 2019. https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf, p. 11.

9 "ICER Myasthenia Gravis Public Comment." ICER. ICER, April 2, 2021. https://icer.org/wp-content/uploads/2021/03/ICER_Myasthenia-Gravis_Public-Comment-Folio_091021.pdf.

10 Ibid.

11 "Rare Disease Day: Frequently Asked Questions." Rare Disease Day, 2019. https://rarediseases.org/wp-content/uploads/2019/01/RDD-FAQ-2019.pdf.

12 "Rare and Special Diseases." AOP Orphan. Accessed October 1, 2021. https://www.aoporphan.com/global_en/rare-diseases.

13 "The Impact of a Rare Disease Diagnosis on Mental Health." PRA Health Sciences, July 19, 2021. https://prahs.com/insights/impact-rare-disease-diagnosis-mental-health.

14 Gomez, Jacy. "Marking Rare Disease Day 2021." Biotechnology Innovation Organization, February 26, 2021. https://www.bio.org/blogs/marking-rare-disease-day-2021.

15 Lemesh, Cindy, Camille Harper, Thomas Purvis, Christopher Tarbell, Steven Zerebecki, Elise Stein, and Genevieve Nowolinski. "The Orphan Drug Act Implementation and Impact." HHS OIG. Department of Health and Human Services, May 2001. https://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf.

16 Greenwood, James. "The Orphan Drug Act Is a Win for Patients and Innovation." LinkedIn. LinkedIn, February 28, 2019. https://www.linkedin.com/pulse/orphan-drug-act-win-patients-innovation-james-greenwood/.

17 Figueiredo, Marta. "Long-Term Onpattro Use Safely Halts FAP Progression, Phase 2 Data Show." FAP News Today, July 21, 2020. https://fapnewstoday.com/2020/07/21/long-term-onpattro-safely-halts-or-reverses-progression-in-fap-patients-final-phase-2-data/.

18 "What Is Fap?" FAP News Today, June 11, 2021. https://fapnewstoday.com/what-is-familial-amyloid-polyneuropathy/.

19 Vardi, Nathan. "Covid's Forgotten Hero: The Untold Story Of The Scientist Whose Breakthrough Made The Vaccines Possible." Forbes. Forbes Magazine, August 17, 2021. https://www.forbes.com/sites/nathanvardi/2021/08/17/covids-forgotten-hero-the-untold-story-of-the-scientist-whose-breakthrough-made-the-vaccines-possible/?sh=4cf51cb0354f.

20 EvaluatePharma Orphan Drug Report 2015. EvaluatePharma, October 2015. http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD15.pdf.

21 Lopata, Erin, Christopher Terrone, Ami Gopalan, Nicholas Ladikos, and Terry Richardson. "Meeting the affordability challenges posed by orphan drugs: a survey of payers, providers, and employers." Journal of Managed Care & Specialty Pharmacy 27, no. 6 (June 2021): 706–13. https://www.jmcp.org/doi/pdf/10.18553/jmcp.2021.20553.

22 "What Is HTA? What Is ISPOR's Health Technology Assessment Central?" Health Technology Assessment Central. Accessed September 27, 2021. https://www.htacentral.org/what-is-hta/.

23 Wong, Jennifer. "The History of Technology Assessment and Comparative Effectiveness Research for Drugs and Medical Devices and the Role of the Federal Government." Biotechnology Law Report. Mary Ann Liebert, Inc., December 1, 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4270161/.

24 Banta, David, and Egon Jonsson. "History of HTA: Introduction." Cambridge Core. Cambridge University Press, July 1, 2009. https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care/article/history-of-hta-introduction/8CBAFF870BC84180B77375205C42BC59.

25 "The International Network of Agencies for Health Technology Assessment." INAHTA. Accessed November 9, 2021. https://www.inahta.org/.

26 "Health Technology Assessment Process: Fundamentals." EUPATI. https://toolbox.eupati.eu/resources/health-technology-assessment-process-fundamentals/.

27 Dintsios, C. M., F. Worm, J. Ruof, and M. Herpers. "Different Interpretation of Additional Evidence for HTA by the Commissioned HTA Body and the Commissioning Decision Maker in Germany: Whenever Iqwig and Federal Joint Committee Disagree." Health Economics Review. Springer Berlin Heidelberg, December 17, 2019. https://healtheconomicsreview.biomedcentral.com/articles/10.1186/s13561-019-0254-6#Sec8.

28 "Health Technology Assessment." PAHO/WHO | Pan American Health Organization. Accessed September 27, 2021. https://www.paho.org/en/topics/health-technology-assessment.

29 Mulligan, Karen, Darius Lakdawalla, Dana Goldman, Jakub Hlávka, Desi Peneva, Martha Ryan, Peter Neumann, Gail Wilensky, and Ruth Katz. "Health Technology Assessment for the U.S. Healthcare System." USC Schaeffer, February 26, 2020. https://healthpolicy.usc.edu/research/health-technology-assessment-for-the-u-s-healthcare-system/.

30 Vreman, Rick A., Aukje K. Mantel-Teeuwisse, Anke M. Hövels, Hubert G.M. Leufkens, and Wim G. Goettsch. "Differences in Health Technology Assessment Recommendations among European Jurisdictions: The Role of Practice Variations." Value in Health. Elsevier, January 14, 2020. https://www.sciencedirect.com/science/article/pii/S1098301519323411.

31 "Barriers to Rare Disease Diagnosis, Care and Treatment In the US: A 30-Year Comparative Analysis." NORD National Organization for Rare Diseases, November 19, 2020. https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf.

32 Rajasimha, Harsha Karur, Prasannakumar Basayya Shirol, Preveen Ramamoorthy, Madhuri Hegde, Sangeeta Barde, Vijay Chandru, M. E. Ravinandan, et al. "Organization for Rare Diseases India (ORDI) - addressing the challenges and opportunities for the Indian rare diseases' community." The National Center for Biotechnology Information. Cambridge University Press, August 13, 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7044965/.

33 Tice JA, Mandrik O, Thokala P, Fotheringham J, Agboola F, HerronSmith S, Chapman R, Pearson SD. Voclosporin and Belimumab for Lupus Nephritis: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, April 16, 2021. https://icer.org/wp-content/uploads/2020/11/ICER_Lupus-Nephritis_Final-Evidence-Report_041621.pdf.

34 "Lupus and Kidney Disease (Lupus Nephritis)." National Institute of Diabetes and Digestive and Kidney Diseases. U.S. Department of Health and Human Services, January 2017. https://www.niddk.nih.gov/health-information/kidney-disease/lupus-nephritis.

35 Korbet, Stephen M., Melvin M. Schwartz, Joni Evans, and Edmund J. Lewis. "Severe Lupus Nephritis: Racial Differences in Presentation and Outcome." American Society of Nephrology. American Society of Nephrology, January 1, 2007. https://jasn.asnjournals.org/content/18/1/244.

36 Ibid.

37 "Kawasaki Disease." Genetic and Rare Diseases Information Center. U.S. Department of Health and Human Services, March 9, 2017. https://rarediseases.info.nih.gov/diseases/6816/kawasaki-disease/cases/21282.

38 Nestler-Parr, Sandra, Daria Korchagina, Mondher Toumi, Chris L. Pashos, Christopher Blanchette, Elizabeth Molsen, Thomas Morel, et al. "Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group." Value in Health. Elsevier, May 2018. https://www.sciencedirect.com/science/article/pii/S1098301518302742.

39 Rudolf, Christopher. "Solving the problem of rare disease heterogeneity with good data." LinkedIn. LinkedIn, January 8, 2021. https://www.linkedin.com/pulse/solving-problem-rare-disease-heterogeneity-good-data-rudolf.

40 Oh, Shin J, Marla B Morgan, Liang Lu, Yuki Hatanaka, Shoji Hemmi, Angela Young, and Gwendolyn C Claussen. "Racial Differences in Myasthenia Gravis in Alabama." NCBI. U.S. National Library of Medicine, March 2009. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2814330/.

41 "Showcase: Rare Disease: Tackling the Barriers to Rare Disease Treatments." PharmaVOICE, February 2021. https://www.pharmavoice.com/article/2021-02-rare-disease-treatments/.

42 "Orphan Drugs in the United States." IQVIA, December 2020. https://www.iqvia.com/insights/the-iqvia-institute/reports/orphan-drugs-in-the-united-states-rare-disease-innovation-and-cost-trends-through-2019.

43 Ibid.

44 Chua, Kao-Ping, and Rena M. Conti. "Trends in Orphan Drug Spending and Out-of-Pocket Spending Among US Children, 2013–18: Health Affairs Journal." Health Affairs, October 2020. https://www.healthaffairs.org/doi/10.1377/hlthaff.2020.00595.

45 DiMasi, Joseph A., Henry G. Grabowski, and Ronald W. Hansen. "Innovation in the pharmaceutical industry: New estimates of R&D costs." Journal of Health Economics. U.S. National Library of Medicine, May 2016. https://pubmed.ncbi.nlm.nih.gov/26928437/.

46 Goodman, Clifford. "HTA 101: II. Fundamental Concepts." U.S. National Library of Medicine. National Institutes of Health, March 7, 2017. https://www.nlm.nih.gov/nichsr/hta101/ta10104.html.

47 Nestler-Parr, Sandra, Daria Korchagina, Mondher Toumi, Chris L. Pashos, Christopher Blanchette, Elizabeth Molsen, Thomas Morel, et al. "Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group." Value in Health. Elsevier, May 2018. https://www.sciencedirect.com/science/article/pii/S1098301518302742.

48 Ibid.

49 Biau, D.J., Kernéis, S. & Porcher, R. Statistics in Brief: The Importance of Sample Size in the Planning and Interpretation of Medical Research. Clin Orthop Relat Res 466, 2282–2288 (2008). https://doi.org/10.1007/s11999-008-0346-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2493004/.

50 Rees, Chris A., Natalie Pica, Michael C. Monuteaux, and Florence T. Bourgeois. "Noncompletion and nonpublication of trials studying rare diseases: A cross-sectional analysis." PLOS Medicine. Public Library of Science, November 21, 2019. https://journals.plos.org/plosmedicine/article?id=10.1371%2Fjournal.pmed.1002966.

51 Ibid.

52 Moloney, Rachael, Penny Mohr, Emma Hawe, Koonal Shah, Martina Garau, and Adrian Towse. "Payer Perspectives on Future Acceptability of Comparative Effectiveness and Relative Effectiveness Research: International Journal of Technology Assessment in Health Care." Cambridge University Press, July 14, 2015. https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care/article/payer-perspectives-on-future-acceptability-of-comparative-effectiveness-and-relative-effectiveness-research/1FD92EF5A8177495DAAA2AB27A08F585.

53 Mitani, Aya, and Sebastien Haneuse. "Small Data Challenges of Studying Rare Diseases." JAMA Network Open. JAMA Network, March 23, 2020. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2763223.

54 Nestler-Parr, Sandra, Daria Korchagina, Mondher Toumi, Chris L. Pashos, Christopher Blanchette, Elizabeth Molsen, Thomas Morel, et al. "Challenges in Research and Health Technology Assessment of Rare DISEASE Technologies: Report of the ISPOR Rare Disease Special Interest Group." Value in Health. Elsevier, May 2018. https://www.sciencedirect.com/science/article/pii/S1098301518302742#bib73.

55 "Surrogate Endpoint." National Cancer Institute, n.d. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/surrogate-endpoint.

56 Belin, Lisa, Aidan Tan, Yann De Rycke, and Agnès Dechartres. "Progression-Free survival as a surrogate for overall survival in oncology trials: a methodological systematic review." British Journal of Cancer. Nature Publishing Group, March 26, 2020. https://www.nature.com/articles/s41416-020-0805-y.

57 Ciani, Oriana, Bogdan Grigore, Hedwig Blommestein, Saskia de Groot, Meilin Möllenkamp, Stefan Rabbe, Rita Daubner-Bendes, and Rod S. Taylor. "Validity of Surrogate Endpoints and Their Impact on Coverage Recommendations: A Retrospective Analysis across International Health Technology Assessment Agencies." SAGE Journals. Society for Medical Decision Making, March 10, 2021, p.449. https://journals.sagepub.com/doi/full/10.1177/0272989X21994553.

58 Bai, Jane P. F., Jeffrey S. Barrett, Gibert J. Burckart, Bernd Meibohm, Hari Cheryl Sachs, and Lynne Yao. "Strategic Biomarkers for Drug Development in Treating Rare Diseases and Diseases in Neonates and Infants." The AAPS journal. Springer US, 19 January 2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3675740/.

59 "How Many People Have Fabry Disease?" National Fabry Disease Foundation. National Fabry Disease Foundation. Accessed October 18, 2021. https://www.fabrydisease.org/index.php/about-fabry-disease/how-many-people-have-fabry-disease.

60 Keating, Gillian, and Dene Simpson. "Agalsidase Beta: a review of its use in the management of Fabry disease." Drugs. U.S. National Library of Medicine, September 18, 2012. https://pubmed.ncbi.nlm.nih.gov/17335299/.

61 Whittal, Amanda, Michela Meregaglia, and Elena Nicod. "The Use of Patient-Reported Outcome Measures in Rare Diseases and Implications for Health Technology Assessment." Springer Link. Springer International Publishing, January 19, 2021. https://link.springer.com/article/10.1007/s40271-020-00493-w.

62 "CDER Patient-Focused Drug Development." U.S. Food and Drug Administration. FDA, July 27, 2021. https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.

63 "Our Patient Engagement Program." ICER. Accessed October 18, 2021. https://icer.org/our-approach/methods-process/patient-engagement/.

64 Whittal, Amanda, Michela Meregaglia, and Elena Nicod. "The Use of Patient-Reported Outcome Measures in Rare Diseases and Implications for Health Technology Assessment." Springer Link. Springer International Publishing, January 19, 2021. https://link.springer.com/article/10.1007/s40271-020-00493-w.

65 Ibid.

66 Kozlov, Natalie, and Honorio Benzon. "Role of Gender and Race in Patient-Reported Outcomes and Satisfaction." Anesthesiology clinics. U.S. National Library of Medicine, June 2020. https://pubmed.ncbi.nlm.nih.gov/32336393/.

67 Nicod, Elena, Lieven Annemans, Anna Bucsics, Anne Lee, Sheela Upadhyaya, and Karen Facey. "HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries." ScienceDirect. Elsevier, February 2019. https://www.sciencedirect.com/science/article/pii/S0168851017300842.

68 "Cost-Effectiveness, the QALY, and the evLYG." ICER, May 21, 2021. https://icer.org/our-approach/methods-process/cost-effectiveness-the-qaly-and-the-evlyg/.

69 Ibid.

70 Rand, Leah, and Aaron Kesselheim. "Controversy over Using Quality-Adjusted Life-Years in Cost-Effectiveness Analyses: A Systematic Literature Review." Health Affairs, September 2021. https://www.healthaffairs.org/doi/10.1377/hlthaff.2021.00343.

71 Nicod, Elena, Lieven Annemans, Anna Bucsics, Anne Lee, Sheela Upadhyaya, and Karen Facey. "HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries." ScienceDirect. Elsevier, February 2019. https://www.sciencedirect.com/science/article/pii/S0168851017300842.

72 Zhou FF, Ward K, Kennedy A, Roberts TS, Gaebler JA. Value for Whom?: Incorporating Patient Perspectives into Value Assessment for Novel Cell and Gene Therapies. Health Advances. 2020. http://www.pipcpatients.org/uploads/1/2/9/0/12902828/cgt_therapies_webinar_draft_final.pdf.

73 Ibid.

74 Gomez, Jacy. "Marking Rare Disease Day 2021." Biotechnology Innovation Organization, February 26, 2021. https://www.bio.org/blogs/marking-rare-disease-day-2021.

75 Augustine, Erika, Heather Adams, and Jonathan Mink. "Clinical Trials in Rare Disease: Challenges and Opportunities." NCBI. Journal of Child Neurology, September 2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3964003/.

76 Pavan, Sonia, Kathrin Rommel, María Elena Mateo Marquina, Sophie Höhn, Valérie Lanneau, and Ana Rath. "Clinical Practice Guidelines for Rare Diseases: The Orphanet Database." PloS one. Public Library of Science, January 18, 2017. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5242437/.

77 Reckers-Droog, Vivian, Job van Exel, and Werner Brouwer. "Willingness to Pay for Health-Related Quality of Life Gains in Relation to Disease Severity and the Age of Patients." ScienceDirect. Elsevier, April 29, 2021. https://www.sciencedirect.com/science/article/pii/S1098301521001455.

78 Rand, Leah, and Aaron Kesselheim. "Controversy over Using Quality-Adjusted Life-Years in Cost-Effectiveness Analyses: A Systematic Literature Review." Health Affairs, September 2021. https://www.healthaffairs.org/doi/10.1377/hlthaff.2021.00343.

79 "Quality-Adjusted Life Years and the Devaluation of Life with Disability." National Council on Disability, November 6, 2019. https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf, p. 11.

80 Neri, Luca, Vincenzina Lucidi, Paola Catastini, and Carla Colombo. "Caregiver burden and vocational participation among parents of adolescents with Cf." Wiley Online Library. Pediatric Pulmonology, March 2016. https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.23352.

81 Jena Anupam and Darius Lakdawalla. "Value Frameworks for Rare Diseases: Should They Be Different?: Health Affairs Blog." Health Affairs, April 12, 2017. https://www.healthaffairs.org/do/10.1377/hblog20170412.059563/full/.

82 N. Bonner, Hall R, Tritton T, Grimes R, Trennery C, Spencer H, and Bennett B. "Rare diseases, are caregivers just as affected as patients?" RTI Health Solutions, October 2017. https://www.rtihs.org/publications/rare-diseases-are-caregivers-just-affected-patients.

83 "The State of Health Disparities in the United States." Communities in Action: Pathways to Health Equity. National Academies Press, January 11, 2017. https://www.ncbi.nlm.nih.gov/books/NBK425844/.

84 "Quality-Adjusted Life Years and the Devaluation of Life with Disability." National Council on Disability, November 6, 2019. https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf, p. 11.

85 "ICER Myasthenia Gravis Public Comment." ICER. ICER, April 2, 2021. https://icer.org/wp-content/uploads/2021/03/ICER_Myasthenia-Gravis_Public-Comment-Folio_091021.pdf.

86 "Quality-Adjusted Life Years and the Devaluation of Life with Disability." National Council on Disability, November 6, 2019. https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf, p. 11.

87 "ICER Myasthenia Gravis Public Comment." ICER. ICER, April 2, 2021. https://icer.org/wp-content/uploads/2021/03/ICER_Myasthenia-Gravis_Public-Comment-Folio_091021.pdf.

88 "RE: Argenx Response to ICER's Draft Scoping on the Assessment of Treatments for Myasthenia Gravis." ICER. argenx, April 2, 2021. https://icer.org/wp-content/uploads/2021/03/ICER_Myasthenia-Gravis_Public-Comment-Folio_041221.pdf.

89 Ibid.

90 Mulligan, Karen, Darius Lakdawalla, Dana Goldman, Jakub Hlávka, Desi Peneva, Martha Ryan, Peter Neumann, Gail Wilensky, and Ruth Katz. "Health Technology Assessment for the U.S. Healthcare System." USC Schaeffer, February 26, 2020. https://healthpolicy.usc.edu/research/health-technology-assessment-for-the-u-s-healthcare-system/.

91 "Cost-Effectiveness, the QALY, and the evLYG." ICER, May 21, 2021. https://icer.org/our-approach/methods-process/cost-effectiveness-the-qaly-and-the-evlyg/.

92 "Modifications to the ICER Value Assessment Framework for Treatments for Ultra-Rare Diseases." ICER, November 2017. https://icer.org/wp-content/uploads/2020/10/ICER_URD_Framework_Adapt_013120.pdf.

93 "ICER's Growing Influence on Payer Decision Making: The Impact of ICER Assessments on Market Dynamics and Patient Access." Xcenda, November 2, 2020. https://www.xcenda.com/insights/htaq-winter-2020-icer-payer-decision-making.

94 Ibid.

95 Gammie, Todd, Christine Y. Lu, and Zaheer Ud-Din Babar. "Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries." PLoS One, October 9, 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4599885/.

96 Allen, Nicola, Stuart R. Walker, Lawrence Liberti, and Sam Salek. "Health Technology Assessment (HTA) Case Studies: Factors Influencing Divergent HTA Reimbursement Recommendations in Australia, Canada, England, and Scotland." Value in Health. Value in Health Journal, December 22, 2016. https://www.valueinhealthjournal.com/article/S1098-3015(16)30019-5/fulltext.

97 "Germany: The Global Guide to Market Access." GLOBALHealthPR, November 19, 2020. https://www.globalhealthpr.com/services/germany/.

98 Ibid.

99 Wenzl, Martin, and Valerie Paris. "Pharmaceutical Reimbursement and Pricing in Germany." OECD, June 2018. https://www.oecd.org/health/health-systems/Pharmaceutical-Reimbursement-and-Pricing-in-Germany.pdf.

100 Bouslouk, Meriem. "G-BA benefit assessment of new orphan drugs in Germany: the first five years." Taylor & Francis, March 14, 2016. https://www.tandfonline.com/doi/full/10.1517/21678707.2016.1166950.

101 Kelly, Steven, Ioanna Stefani, Charlotte Poon, and Nimisha Raj. "Comparison of health technology assessments and time to reimbursement for Orphan Drugs." European Pharmaceutical Review, July 2020. https://www.europeanpharmaceuticalreview.com/article/122521/comparison-of-health-technology-assessments-and-time-to-reimbursement-for-orphan-drugs/.

102 Heyes, Anne, D. McBride, I. Pearson, and K. Copley-Merriman. "HTA and Reimbursement Considerations for Rare Diseases in European Markets: What Are the Implications for Manufacturers?" RTI Health Solutions, November 2018.https://www.rtihs.org/sites/default/files/29385%20Heyes%202018%20HTA%20and%20reimbursement%20considerations%20for%20rare%20diseases%20in%20European%20markets%20what%20are%20the%20implications%20for%20manufacturers.pdf.

103 Kelly, Steven, Ioanna Stefani, Charlotte Poon, and Nimisha Raj. "Comparison of health technology assessments and time to reimbursement for Orphan Drugs." European Pharmaceutical Review, July 2020. https://www.europeanpharmaceuticalreview.com/article/122521/comparison-of-health-technology-assessments-and-time-to-reimbursement-for-orphan-drugs/.

104 Kirchmann, Tim, Heike Kielhorn-Schönermark, and Matthias P. Schönermark. "White Paper: Orphan Drugs in Germany – lessons learned from AMNOG, best and worst practices and strategic implications." SKC-Beratung, 2017. https://skc-beratung.de/wp-content/uploads/2017/03/White_Paper_SKC.pdf.

105 Ibid.

106 Jaksa, Ashley. "The case for real-world evidence in Germany." Aetion, August 29, 2019. https://aetion.com/evidence-hub/the-case-for-real-world-evidence-in-germany/.

107 "The GSAV Has Been Officially Integrated into the Rules of Procedure of the G-BA." SKC Beratungsgesellschaft, August 24, 2020. https://skc-beratung.de/insights/blog/2020/08/GSAV_Rules_of_Procedure_G-BA.php.

108 Stawowczyk, Ewa, Krzysztof Piotr Malinowski, Paweł Kawalec, Rafał Bobiński, Jacek Siwiec, Dimitra Panteli, Helene Eckhardt, et al. "Reimbursement Status and Recommendations Related to Orphan Drugs in European Countries." Frontiers. Frontiers in Pharmacology, November 27, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6890830/.

109 Ibid.

110 "What is the incremental cost-effectiveness ratio (ICER)?" GaBi Generics and Biosimilars Initiative, March 12, 2010. https://www.gabionline.net/generics/general/What-is-the-incremental-cost-effectiveness-ratio-ICER.

111 Kamae, Isao, Rob Thwaites, Anna Hamada, and Jovelle L. Fernandez. "Health technology assessment in Japan: a work in progress." Taylor & Francis Online. Journal of Medical Economics, January 29, 2020. https://www.tandfonline.com/doi/full/10.1080/13696998.2020.1716775.

112 Tchebaniouk, Elizaveta. "Japan Incorporates Cost-Effectiveness Into Its HTA: What Manufacturers Can Do to Prepare." Windrose Consulting Group, n.d. https://windrosecg.com/news-events/2021/7/1/japan-incorporates-cost-effectiveness-into-its-hta-what-manufacturers-can-do-to-prepare.

113 Kamae, Isao, Rob Thwaites, Anna Hamada, and Jovelle L. Fernandez. "Health technology assessment in Japan: a work in progress." Taylor & Francis Online. Journal of Medical Economics, January 29, 2020. https://www.tandfonline.com/doi/full/10.1080/13696998.2020.1716775.

114 Blonda, Alessandra, Yvonne Denier, Isabelle Huys, and Steven Simoens. "How to Value Orphan Drugs? A Review of European Value Assessment Frameworks." Frontiers. Frontiers in Pharmacology, May 12, 2021. https://www.frontiersin.org/articles/10.3389/fphar.2021.631527/full.

115 Tchebaniouk, Elizaveta. "Japan Incorporates Cost-Effectiveness Into Its HTA: What Manufacturers Can Do to Prepare." Windrose Consulting Group, n.d. https://windrosecg.com/news-events/2021/7/1/japan-incorporates-cost-effectiveness-into-its-hta-what-manufacturers-can-do-to-prepare.

116 Smith, William S. "The U.S. shouldn't use the "QALY: in drug cost-effectiveness reviews." STAT, February 22, 2019. https://www.statnews.com/2019/02/22/qaly-drug-effectiveness-reviews/.

117 Matar, Marc, Graham Tatham, Sam Calderwood, and Shavinder Girn. "NICE's Highly Specialized Technologies." Simon-Kucher & Partners, January 5, 2021. https://www.simon-kucher.com/en-us/blog/nices-highly-specialized-technologies.

118 Nicod, Elena, Lieven Annemans, Anna Bucsics, Anne Lee, Sheela Upadhyaya, and Karen Facey. "HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries." ScienceDirect. Elsevier, February 2019. https://www.sciencedirect.com/science/article/pii/S0168851017300842.

119 Ibid.

120 Matar, Marc, Graham Tatham, Sam Calderwood, and Shavinder Girn. "NICE's Highly Specialized Technologies." Simon-Kucher & Partners, January 5, 2021. https://www.simon-kucher.com/en-us/blog/nices-highly-specialized-technologies.

121 "Technology appraisal guidance." NICE. National Institute for Health and Care Excellence, n.d. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance.

122 Matar, Marc, Graham Tatham, Sam Calderwood, and Shavinder Girn. "NICE's Highly Specialized Technologies." Simon-Kucher & Partners, January 5, 2021. https://www.simon-kucher.com/en-us/blog/nices-highly-specialized-technologies.

123 Mwamburi M, Nanavaty M, Gala S, Nyandege A, Ramesh V. "Provisions and Special Considerations for Rare Diseases/Orphan Drugs by Health Technology Assessment (HTA) Bodies: Systematic Evaluation in 25 Countries." Value in Health Journal, 2016. https://www.valueinhealthjournal.com/article/S1098-3015(16)32837-6/pdf.

124 Stawowczyk, Ewa, Krzysztof Piotr Malinowski, Paweł Kawalec, Rafał Bobiński, Jacek Siwiec, Dimitra Panteli, Helene Eckhardt, et al. "Reimbursement Status and Recommendations Related to Orphan Drugs in European Countries." Frontiers. Frontiers in Pharmacology, November 27, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6890830/.

125 Clarke, Sophie, Michelle Ellis, and Jack Brownrigg. "The Impact of Rarity in Nice's Health Technology Appraisals." Orphanet Journal of Rare Diseases. BioMed Central, May 13, 2021. https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01845-x.

126 Zamora, Bernarda, Francois Maignen, Phill O'Neill, Jorge Mestre-Ferrandiz, and Martina Garau. "Comparing access to orphan medicinal products in Europe." Orphanet Journal of Rare Diseases. BioMed Central, May 3, 2019. https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1078-5.

127 M, Prada, Mariano EE, and Candelora L. "PRO76: Italian 648/96 Law Application between Jan 2013 and September 2019: Focus on Orphan Drugs." Medvance, November 2019. https://medvance.eu/wp-content/uploads/2019/11/Intexo_ISPOR-Prada-et-al-2019-648.pdf.

128 Ibid.

129 Zamora, Bernarda, Francois Maignen, Phill O'Neill, Jorge Mestre-Ferrandiz, and Martina Garau. "Comparing access to orphan medicinal products in Europe." Orphanet Journal of Rare Diseases. BioMed Central, May 3, 2019. https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1078-5.

130 Ibid.

131 "Law 648/1996." Italian Medicines Agency, n.d. https://www.aifa.gov.it/en/legge-648-96.

132 "Health Technology Assessment, Price and Reimbursement Review for Orphan Drugs in Italy." Value in Health Journal, 2014. https://www.valueinhealthjournal.com/article/S1098-3015(14)03663-8/pdf.

133 Gammie, Todd, Christine Y. Lu, and Zaheer Ud-Din Babar. "Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries." PLoS One, October 9, 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4599885/.

134 Zamora, Bernarda, Francois Maignen, Phill O'Neill, Jorge Mestre-Ferrandiz, and Martina Garau. "Comparing access to orphan medicinal products in Europe." Orphanet Journal of Rare Diseases. BioMed Central, May 3, 2019. https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1078-5.

135 Ibid.

136 "Cystic Fibrosis FAQs." Cystic Fibrosis Trust, n.d. https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/faqs.

137 Ibid.

138 "Orkambi (Ivacaftor/lumacaftor)." Cystic Fibrosis News Today, n.d. https://cysticfibrosisnewstoday.com/orkambi-lumacaftor-ivacaftor-vertex/.

139 Sagonowsky, Eric, and Eric Palmer. "UPDATED: NICE sticks to its guns and turns down Vertex's Orkambi even as patients plead." FiercePharma, June 16, 2016. https://www.fiercepharma.com/pharma/cystic-fibrosis-trust-issues-orkambi-access-plea-vertex-nice.

140 "Cost of cystic fibrosis treatment too high for benefit offered, says NICE." NICE. National Institute for Health and Care Excellence, June 17, 2016. https://www.nice.org.uk/news/press-and-media/cost-of-cystic-fibrosis-treatment-too-high-for-benefit-offered-says-nice.

141 Sagonowsky, Eric, and Eric Palmer. "UPDATED: NICE sticks to its guns and turns down Vertex's Orkambi even as patients plead." FiercePharma, June 16, 2016. https://www.fiercepharma.com/pharma/cystic-fibrosis-trust-issues-orkambi-access-plea-vertex-nice.

142 Hunt, Jeremy, and Sarah Wollaston. "Correspondence with the Secretary of State for Health and Social Care Orkambi and Cystic Fibrosis." UK Parliament, June 5, 2018. https://www.parliament.uk/globalassets/documents/commons-committees/Health/Correspondence/2017-19/Correspondence-with-the-Secretary-of-State-for-Health-and-Social-Care-Orkambi-and-cystic-fibrosis.pdf.

143 Sagonowsky, Eric, and Eric Palmer. "UPDATED: NICE sticks to its guns and turns down Vertex's Orkambi even as patients plead." FiercePharma, June 16, 2016. https://www.fiercepharma.com/pharma/cystic-fibrosis-trust-issues-orkambi-access-plea-vertex-nice.

144 "Primary-Progressive Multiple Sclerosis (PPMS)." Cedars Sinai, n.d. https://www.cedars-sinai.org/health-library/diseases-and-conditions/p/--primary-progressive-multiple-sclerosis-ppms.html.

145 De Seze, Jerome. "Expecting more for people with PPMS." Roche, n.d. https://www.roche.com/research_and_development/what_we_are_working_on/neuroscience/ms/ms-clinical-advances-ppms.htm.

146 "OCREVUS (Ocrelizumab) Results in Primary Progressive MS (PPMS)." OCREVUS, n.d. https://www.ocrevus.com/patient/ocrevus-101/primary-progressive-multiple-sclerosis.html.

147 "FDA approves Roche's OCREVUS™ (ocrelizumab) for relapsing and primary progressive forms of multiple cclerosis." Roche, March 29, 2017. https://www.roche.com/investors/updates/inv-update-2017-03-29.htm.

148 Armoiry, Xavier, Hans-Martin Späth, Anna-Maria Henaine, Claude Dussart, Carl Counsell, and Martin Connock. "Ocrelizumab not recommended in France for patients with primary progressive multiple sclerosis while recommended in England: a review comparing the assessment by HAS and NICE." National Library of Medicine. Expert Opinion on Biological Therapy, December 24, 2020. https://pubmed.ncbi.nlm.nih.gov/33356643/.

149 "Ocrelizumab for treating primary progressive multiple cclerosis." NICE. National Institute for Health and Care Excellence, June 12, 2019. https://www.nice.org.uk/guidance/TA585/chapter/1-Recommendations.

150 Fromont, Agnes, Christine Binquet, Erik A. Sauleau, Isabelle Fournel, Audrey Bellisario, Johan Adnet, Alain Weill, et al. "Geographic variations of multiple sclerosis in France." OUP Academic. Brain, July 2010. https://academic.oup.com/brain/article/133/7/1889/327700.

151 "Spinal Muscular Atrophy (SMA)" Cleveland Clinic, n.d. https://my.clevelandclinic.org/health/diseases/14505-spinal-muscular-atrophy-sma.

152 "SMA Life Expectancy and Disease Onset." SMA News Today, n.d. https://smanewstoday.com/sma-life-expectancy/#:~:text=Overall%2C%20about%2068%25%20of%20children,in%20respiratory%20and%20nutritional%20care.

153 "SPINRAZA® (Nusinersen) Approved in the European Union as First Treatment for Spinal Muscular Atrophy." Biogen, June 1, 2017. https://investors.biogen.com/news-releases/news-release-details/spinrazar-nusinersen-approved-european-union-first-treatment.

154 Ibid.

155 "U.S. FDA Approves Biogen's SPINRAZA™ (nusinersen), The First Treatment for Spinal Muscular Atrophy." Biogen, December 23, 2016. https://investors.biogen.com/news-releases/news-release-details/us-fda-approves-biogens-spinrazatm-nusinersen-first-treatment.

156 Taylor, Phil. "Shock as NICE turns down Biogen's SMA therapy." PMLiVE, August 14, 2018. http://www.pmlive.com/pharma_news/shock_as_nice_turns_down_biogens_sma_therapy_1248819.

157 McConaghie, Andrew. "'Inflexible' NICE blocking access to rare disease drugs." PMLiVE, February 19, 2019. http://www.pmlive.com/pharma_news/inflexible_nice_blocking_access_to_rare_disease_drugs_1278747.

158 Taylor, Phil. "Shock as NICE turns down Biogen's SMA therapy." PMLiVE, August 14, 2018. http://www.pmlive.com/pharma_news/shock_as_nice_turns_down_biogens_sma_therapy_1248819.

159 Ibid.

160 "New Data Presented at MDA Clinical Conference Show Benefit in Motor Function for Infants, Teens and Young Adults Treated With SPINRAZA® (nusinersen)." Biogen, March 12, 2018. https://investors.biogen.com/news-releases/news-release-details/new-data-presented-mda-clinical-conference-show-benefit-motor.

161 "Nice Announces More People Eligible for Nusinersen Following Review of Managed Access Agreement." NICE, May 4, 2021. https://www.nice.org.uk/news/article/nice-announces-more-people-eligible-for-nusinersen-following-review-of-managed-access-agreement.

162 McConaghie, Andrew. "'Inflexible' NICE blocking access to rare disease drugs." PMLiVE, February 19, 2019. http://www.pmlive.com/pharma_news/inflexible_nice_blocking_access_to_rare_disease_drugs_1278747.

163 Miller, Kathleen, Lewis J. Fermaglich, and Janet Maynard. "Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases." Orphanet Journal of Rare Diseases, June 09, 2021. https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01901-6.

164 DiMasi, Joseph A., Henry G. Grabowski, and Ronald W. Hansen. "Innovation in the pharmaceutical industry: New estimates of R&D costs." Journal of Health Economics. U.S. National Library of Medicine, May 2016. https://pubmed.ncbi.nlm.nih.gov/26928437/.

165 Rep. EvaluatePharma Orphan Drug Report 2015. EvaluatePharma, October 2015. http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD15.pdf.

166 Mitani, Aya, and Sebastien Haneuse. "Small Data Challenges of Studying Rare Diseases." JAMA Network Open. JAMA Network, March 23, 2020. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2763223.

167 Matar, Marc, Graham Tatham, Sam Calderwood, and Shavinder Girn. "NICE's Highly Specialized Technologies." Simon-Kucher & Partners, January 5, 2021. https://www.simon-kucher.com/en-us/blog/nices-highly-specialized-technologies.

168 Ibid.

169 Hunt, Jeremy, and Sarah Wollaston. "Correspondence with the Secretary of State for Health and Social Care Orkambi and Cystic Fibrosis." UK Parliament, June 5, 2018. https://www.parliament.uk/globalassets/documents/commons-committees/Health/Correspondence/2017-19/Correspondence-with-the-Secretary-of-State-for-Health-and-Social-Care-Orkambi-and-cystic-fibrosis.pdf.

170 McConaghie, Andrew. "'Inflexible' NICE blocking access to rare disease drugs." PMLiVE, February 19, 2019. http://www.pmlive.com/pharma_news/inflexible_nice_blocking_access_to_rare_disease_drugs_1278747.

171 Zamora, Bernarda, Francois Maignen, Phill O'Neill, Jorge Mestre-Ferrandiz, and Martina Garau. "Comparing access to orphan medicinal products in Europe." Orphanet Journal of Rare Diseases. BioMed Central, May 3, 2019. https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1078-5.

172 Ibid.

173 "Law 648/1996." Italian Medicines Agency, n.d. https://www.aifa.gov.it/en/legge-648-96.

174 Gomez, Jacy. "Marking Rare Disease Day 2021." Biotechnology Innovation Organization, February 26, 2021. https://www.bio.org/blogs/marking-rare-disease-day-2021.

175 “Marketing Authorisation.” European Medicines Agency. Accessed November 9, 2021. https://www.ema.europa.eu/en/glossary/marketing-authorisation.

176 Goodman, Clifford. “HTA 101: V. Economic Analysis Methods.” U.S. National Library of Medicine. National Institutes of Health, May 2014. https://www.nlm.nih.gov/nichsr/hta101/ta10107.html.

177 Incremental Cost-Effectiveness Ratio (ICER) [online]. (2016). York; York Health Economics Consortium; 2016. https://yhec.co.uk/glossary/incremental-cost-effectiveness-ratio-icer/.

178 “Innovative Medicine.” European Medicines Agency. Accessed November 9, 2021. https://www.ema.europa.eu/en/glossary/innovative-medicine.

179 R, Macaulay. “Managed Access Agreements: A New Model Pathway for The Reimbursement of Non-Oncology Drugs in England Approved Under European Adaptive Pathways?” Value in Health Journal, November 1, 2016. https://www.valueinhealthjournal.com/article/S1098-3015(16)32288-4/fulltext.

180 “Nonrandomized Clinical Trial.” National Cancer Institute. Accessed November 9, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/nonrandomized-clinical-trial.

181 “Orphan Drug.” National Cancer Institute. Accessed November 9, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/orphan-drug.

182 Prieto, Luis, and José A Sacristán. “Problems and Solutions in Calculating Quality-Adjusted Life Years (Qalys).” Health and quality of life outcomes. BioMed Central, December 19, 2003. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC317370/.

183 “Orphan Drug Act – Relevant Excerpts.” U.S. Food and Drug Administration. FDA, March 9, 2018. https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts.

184 Wapner, Jessica. “How Prescription Drugs Get Their Prices, Explained.” Newsweek, March 17, 2017. https://www.newsweek.com/2017/04/14/prescription-drug-pricing-569444.html.

185 Stoppler, Melissa Conrad. “Medical Definition of Standard of Care.” MedicineNet. MedicineNet, March 29, 2021. https://www.medicinenet.com/standard_of_care/definition.htm.

186 Bertram, Melanie, Jeremy Lauer, Kees De Joncheere, Tessa Edejer, Raymond Hutubessy, Marie-Paule Kieny, and Suzanne Hill. “Cost–Effectiveness Thresholds: Pros and Cons.” WHO, 2016. https://www.who.int/bulletin/volumes/94/12/15-164418.pdf.