

Looming Challenges for ICER in Assessing the Value of Rare Disease Therapies

By Dr. William Smith



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Introduction

Led by the United Kingdom's National Institute for Health and Care Excellence (NICE), many developed countries with nationalized healthcare systems have traditionally relied on "cost effectiveness reviews" to rate emerging therapies and make decisions about whether to cover those treatments in their health systems. The NICE methodology utilizes Quality Adjusted Life Years (QALYs) to rate the value of drugs and devices based upon their ability to extend life and to improve the quality of life.

Supporters of the QALY-based reviews argue that they represent an objective and balanced method of assessing the true value of new treatments and provide policymakers with an indispensable cost control tool. Critics of the reviews argue

For the first time, in 2018, over half of new drug approvals were for orphan drugs.

that they are simply a poorly constructed fig leaf to justify rationing and deny treatments to vulnerable populations such as the elderly, the disabled, cancer patients and those with rare diseases. A number of critics see the slow degradation of oncology care in the United Kingdom as the clearest example of the QALY's failure, because Parliament was

forced to ignore the NICE cost effectiveness reviews and pay for cancer drugs regardless of their QALY rating.¹

In the United States, the Institute for Clinical and Economic Review (ICER) is working to bring these European-style cost effectiveness reviews to commercial and government payers. Like NICE, ICER employs the QALY methodology. During consideration of the Affordable Care Act, Congress worried about the impact of these reviews on the elderly and disabled and made it illegal to utilize the QALY methodology in cost effectiveness reviews for the Medicare program. ICER's ambition is therefore to have state Medicaid programs and commercial plans employ their reviews when making coverage decisions. CVS Caremark, the nation's second largest pharmacy benefit manager, recently announced that it would employ QALY-based analysis to assist clients in lowering drug costs, although it is unclear if the company still intends to move forward with the plan.²

There is significant academic literature on the limitations of the QALY methodology and its potential adverse impacts upon various patient populations.³ This paper will focus on the potential obsolescence of the QALY methodology in conducting cost effectiveness reviews on the most rapidly growing sector of the biopharmaceutical marketplace: therapies for rare and orphan diseases.

The Changing Biopharmaceutical Marketplace

For a variety of complex policy, legal, regulatory and scientific reasons, the pharmaceutical marketplace has witnessed

a dramatic change of direction in recent decades. FDA approvals for new orphan drugs⁴ or new orphan indications have exploded. For example, FDA-approved orphan indications grew from two in 1983 to 80 in 2017. As the IQVIA Institute pointed out: "In just 2017 alone, the FDA granted orphan designations to over 429 unique drugs under development."⁵ The laboratories of biopharmaceutical companies are increasingly focused on orphan drugs and for the first time, in 2018, over half of new drug approvals were for orphan drugs.

A related trend in the biopharmaceutical marketplace is the growth in spending on specialty drugs. Specialty products have no exact definition but are typically drugs that treat complex conditions such as cancer or rheumatoid arthritis and generally are not delivered in pill form but may be infused or injected. Eighty-seven percent of orphan drugs fall into the specialty drug category, but many specialty drugs have patient populations larger than 200,000 and do not enjoy orphan drug status. That said, specialty drugs generally have smaller patient populations, and are more expensive than, traditional small molecule drugs. For example, while an estimated 1.3 million people in the U.S. suffer from rheumatoid arthritis that is typically treated with specialty medicines, 95 million Americans have high cholesterol that is typically treated with traditional small molecule medicines.^{6,7}

Specialty drugs, with orphan drugs as a subcategory, are responsible for the lion's share of spending on new drugs. In 2017, for example, net new spending on branded drugs was \$12 billion with specialty medicines making up \$9.7 billion of that total. Of the 42 new medicines launched during 2017, 32 were specialty drugs.⁸ Both specialty and orphan drugs are considerably more expensive than traditional medicines with one study predicting that by 2023, the median annual prices of orphan and oncology drugs will be "well above" \$100,000.⁹ The trend toward specialty and orphan drugs has been quite pronounced in recent years. The specialty share of drug spending has grown from 11 percent in 1997 to 43 percent in 2017, while orphan drug spending grew from 4 percent to 11 percent over the same period.¹⁰

It should be noted that despite the higher prices for specialty and orphan drugs, there are data to suggest that the U.S. healthcare system is able to sustain these prices because many traditional "blockbuster" small molecule medicines, such as Lipitor to treat high cholesterol, have gone off patent, generating enormous savings for the system.¹¹ Patent expirations will provide \$95 billion in cost savings to the U.S. market by 2023, with \$26 billion in savings coming in 2019 alone. These savings from patent losses are so large because generic prescribing has increased dramatically. When doctors prescribe medicines for chronic conditions, about 90 percent of the time, patients will receive a generic drug, i.e. a traditional medicine that has gone off patent.¹² In other words, an accurate assessment of pharmaceutical spending growth should weigh the increases

observed in speciality drug spending against the decreases in spending for small molecules. In short, for the foreseeable future, the growth in specialty and orphan drugs will not be an undue burden upon the healthcare system. Specialty spending should also be weighed in the context of the level of innovation being brought to market. Many new specialty products offer breakthrough efficacy to patient populations that previously had few and suboptimal treatment options. The value to the patient of gene therapies for hereditary blindness or spinomuscular atrophy should not be underestimated.

Implications for Cost Effectiveness Reviews

Since most of the growth in medicine spending is coming in the area of specialty and orphan drugs, we must ensure that cost effectiveness reviews are particularly well suited to evaluating drugs for smaller patient populations with complex and rare diseases. The question this paper seeks to address is: do traditional European style cost effectiveness reviews, such as ICER's use of QALYs, lend themselves well to evaluating these new drugs?

Before 2017, even ICER itself would have answered this question in the negative as they launched a review to revise their framework for evaluating “ultra-rare” diseases. In a press release requesting public comment on a revised framework to evaluate drugs for rare diseases, ICER acknowledged the unique challenges inherent in evaluating the growing number of drugs for complex diseases for smaller patient populations.¹³ ICER wanted its revised framework for these drugs to reflect “the distinctive practical and ethical challenges associated with potential major advances for serious ultra-rare conditions.”

The Traditional ICER Cost Effectiveness Framework

Before we explore ICER's revised framework for rare disease drugs, we should examine its traditional framework. As with NICE in the UK, the bedrock methodology of the ICER framework is the QALY. A QALY rating combines two measurements of a drug's effectiveness into a single score: the drug's ability to prolong life and its ability to improve the quality of life. As explained by scholars in the *British Medical Bulletin*: “The QALY is able to combine the effects of health interventions on mortality and morbidity into a single index, thereby providing a ‘common currency’ to enable comparisons across different disease areas.”¹⁴

QALY methodology ranks quality of life on a scale of 0 to 1, with zero being death and 1 being a year lived in perfect health. For example, if a drug provides a quality of life ranked at .5, this is multiplied by the drug's longevity score. So, a drug with a .5 quality of life score that provided for 4 additional years of life would receive a QALY score of 2 QALYs (.5 x 4).

This score can then be compared with other treatments in the same category as well as with treatments for other conditions to evaluate the “value” of a new drug.

ICER's methodology then incorporates a “threshold” monetary value of a year of life lived in perfect health. To establish this threshold, ICER adopts a recommendation of the World Health Organization (WHO) “which suggests a threshold range of 1–3 times the per capita GDP of the country per additional QALY. For the US, this translates to \$57,000 to \$171,000 per QALY gained, which is in close proximity to ICER's threshold of \$50,000 to \$175,000 per QALY gained.”¹⁵

By combining a drug's longevity/quality of life score with the monetary threshold amounts, ICER can recommend the relative value of different therapies. Therefore, a drug that can provide a full year of life lived in perfect health for \$50,000 or less is considered a “high value” treatment. A drug costing more than \$175,000 provides for “low value” and a drug costing between \$50,000 and \$175,000 represents an “intermediate value” drug.

While there are many questions about the appropriateness of this methodology for rating all pharmaceutical treatments, the QALY is particularly ill-suited to assess the value of rare disease treatments for a variety of reasons discussed below.¹⁶

Thresholds Not Appropriate for Rare Disease Drugs

With the Orphan Drug Act in 1983, Congress recognized that the traditional pharmaceutical business model was not producing enough therapies for rare diseases. The simple economic reason for this scarcity of rare disease drugs was that companies were sinking their substantial R&D investments into therapeutic areas with higher prevalence rates, i.e. more potential customers.

With the Orphan Drug Act, Congress provided greater market exclusivity, tax breaks and other incentives that made R&D investments into rare disease drugs potentially more profitable. So began the trend of more and more drug approvals for rare disease and orphan drugs.

However, while federal law provided the impetus to invent more rare disease drugs, it did not solve the challenge of pricing these drugs. R&D costs for a rare disease drug are quite substantial as finding and enrolling patients in trials are particularly challenging. And with lower prevalence rates, the higher costs are spread over much smaller patient populations, making the price for one course of treatment substantially higher than traditional small molecule drugs for large patient populations.

The QALY is particularly ill-suited to assess the value of rare disease treatments.

Because of the uniqueness of this rare disease model, one 2014 study in the *Journal of Comparative Effectiveness Research* predicted that new cost effectiveness models would need to be developed to account for this rare disease model.¹⁷ Without new models, the study predicted that traditional cost-effectiveness tools would be biased against rare disease drugs, leading to uniformly poor ratings. As the study pointed out, “given the largely fixed (i.e. independent from sales volume) nature of R&D costs, it seems plausible that the issue of not meeting conventional benchmarks for cost-effectiveness will only increase in relevance with decreasing prevalence rates, especially with drugs developed to treat small patient populations.”

This study’s analysis turned out to be quite prescient. By 2018, a study appeared in *Health Affairs* that examined ICER’s 2014–18 reviews of rare disease drugs to ascertain the number of therapies that had been rated as having “high value.”¹⁸ The answer was none. Of the five drugs evaluated to treat diseases for small populations, four were rated of “low value” while one was rated an “intermediate value.”

This trend in the model’s bias against rare disease drugs has continued. A very recent ICER review of two breakthrough therapies for Spinal Muscular Atrophy (SMA), a terrible childhood disease, concluded that neither therapy met “traditional cost-effectiveness thresholds.”¹⁹

One option to revise this bias would be for ICER to raise its QALY thresholds for orphan or rare disease drugs. In general, ICER has refused to take this step as, one might surmise, revising the thresholds based upon certain important contextual factors would open up the entire ICER methodology to the question of why certain key contextual issues for different disease states and patient populations are not built into the model. ICER has, however, created a new “ultra-rare” category of diseases with fewer than 10,000 patients, a category that does not exist in the current U.S. regulatory or legal framework. For this category, as the *Health Affairs* study explains, “ICER also presents in its reports additional cost-effectiveness benchmarks up to \$500,000-per-QALY gained, stating that decision-makers may be willing to consider higher benchmarks in such situations.” In other words, ICER is not raising the QALY threshold of cost-effectiveness to \$500,000, they are merely willing to consider raising it in individual cases. As the recent SMA review demonstrated however, ICER has not implemented a substantially new model for “ultra-rare” disease drugs.

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Clinical Trial Data Too Limited to Evaluate Ultimate Value

Another factor in the emerging biopharmaceutical marketplace portends obsolescence of the QALY model: with the rising number of orphan or rare disease therapies, fewer patients are involved in clinical trials and the dataset is less robust than other traditional drugs. This is particularly the case with what ICER classifies as “ultra-rare disease” drugs (URDs). As the study in the *Journal of Comparative Effectiveness Research* pointed out, less clinical research with URDs means “limited clinical understanding,” fewer physicians with “specialized expertise,” fewer “validated instruments to measure disease severity/progression,” less ability to “accurately diagnose patients with URDs,” and given the small number of patients that are geographically dispersed, “multiple clinical trial sites must be established for only a few patients.”²⁰ In short, it is harder to generate robust clinical data for these diseases and therefore the data are less certain.

There is a contradiction, however, in ICER’s approach to this problem of limited data. When it comes to the clinical value of these therapies, ICER is eager to point out the uncertainty inherent in the data for rare disease drugs. In their recent [review](#) of two SMA therapies, for example, ICER points out that: “First, for both interventions, the narrow eligibility criteria of trials and the limited sample size... raises concerns about generalizability of results to the wider population of patients with SMA... In addition, there is a lack of data on the long-term safety and efficacy of both interventions.”²¹

They go on to point out that, also because of limited data, there is uncertainty about the potential for serious side effects or whether the therapies will be effective over the longer term.

While ICER seems quite eager to point out that because the safety and efficacy data is less robust for these two SMA therapies, their clinical value is less certain. On the other hand, ICER nonetheless seems confident in its assessment that neither drug is cost-effective, and their prices should be far lower. How can one cast doubt on the reliability of the clinical evidence of effectiveness and safety and also confidentially argue that they are overpriced? Isn’t it also possible that the therapies are more effective and safer than the limited data indicate?

For rare disease drugs, rather than discouraging payers from covering these new therapies, as ICER does, would not a more humane and prudent approach be to encourage payers to cover these therapies immediately in order to generate more data and reach a more certain cost-effectiveness conclusion, utilizing real world evidence? In the case of Zolgensma,

Novartis's drug for SMA, ICER issued its conclusion that the drug was not cost-effective on the same day it was approved by the FDA.²² If payers accepted ICER's findings as stated, patients with this devastating condition would have been denied the opportunity to try a treatment that could literally change the course and duration of their lives. ICER seems less eager base its conclusions on robust data than to signal payers that rare disease drugs are not a good value.

The Obsolescence of the ICER Model Will Increase with Genetic Advances

In the future, the practice of medicine will be increasingly personalized, and medicines will be targeted to patients based

upon their genetic makeup. Diagnostic tests, not QALYs, will be able to determine when a medicine will be cost-effective. As one study in the *Journal of Stem Cell Research and Therapy* pointed out: "As we embark on paradigm shift away from conventional medicine and its intuitive "one-size-fits-all" approach toward precision (or personalized) medicine, which utilizes an array of patient metrics including gene expression, metabolomics and predic-

tive biomarkers, there will be an associated decrease in the level of variation in response to treatment."²³

ICER's methodology is, by definition, a "one-size-fits-all" approach that will inevitably fail to keep up with medical science's understanding of how and why different therapies work differently in different patients. Over the long run, these ICER reviews will be unlikely to provide valuable insights into the cost-effectiveness of numerous therapies when those therapies will be understood to present a huge number of variations in patient responses due to a complex genetic and metabolomic factors. As the Biotechnology Industry Organization pointed out in their comments on ICER's proposed framework for ultra-rare diseases: "A QALY distills the entire patient experience for a particular medical intervention into one number. But as the field of personalized medicine advances and interventions can be tailored down to the level of the patient's own genetic code, any rationale for using a QALY in clinical decision-making fails as a framework. ICER's continued use of the QALY in both the Value Framework and in its modified Framework for medicines that treat ultra-rare diseases will undermine the goals of personalized medicine."²⁴

ICER Thresholds Are Arbitrary

The complexity, diversity and severity of orphan and rare diseases present many complex ethical, contextual, and

treatment challenges. The ICER QALY thresholds are arbitrary enough when applied to traditional medicines, but when applied to treatments for rare diseases, they take on an additional—and troubling—arbitrariness.

On what authority does ICER claim that only therapies achieving a QALY of less than \$50,000 are "high value" therapies? The number may be related to a World Health Organization standard but that standard itself is arbitrary. These thresholds are not "scientific" in any economic sense but, in asserting a value on a human life, they are a kind of theological dogma that must be accepted on faith as an objective standard. Yet, the entire superstructure of the QALY methodology is built upon these arbitrary dogmas which, if questioned, render the entire model illegitimate.

The arbitrariness of the QALY thresholds has particularly troubling consequences when they are employed to recommend that rare disease drugs do not deserve coverage unless their prices can be compressed to fit the assumptions of the model. As the *Journal of Comparative Effectiveness Research* study concluded: "QALYs, conceptualized as a preference-based measure of individual health-related outcomes combining quality and length of life, seemingly fail to capture the full social value of URD technologies; hence their need to be complemented or replaced with alternatives that include societal preferences, such as concerns for equity in treatment." Without significant changes to the QALY model, the study concluded that "their application may lead to positively unethical conclusions that might deprive patients with URDs any chance of effective care."

ICER's Definition of "Ultra-Rare Disease" is also Arbitrary

When ICER announced it was developing a revised framework to assess the value of rare disease drugs, one of the greatest disappointments expressed by the patient advocacy community was ICER's arbitrary limitation of the proposed framework to diseases with 10,000 patients or less. This patient population cohort size corresponds to no definitions of rare or ultra-rare diseases under any U.S. legal or regulatory framework. ICER justified the arbitrary nature of the figure by pointing out that it was "modestly higher than the threshold used in the EU."²⁵

Pointing to one arbitrary threshold to justify another was not satisfying to patient advocates. After all, many treatments for rare and devastating diseases would not, it was thought, benefit from the more generous thresholds that the new Framework might provide. For example, patients with two relatively rare and serious diseases, sickle cell disease and hemophilia, may soon benefit from gene therapies to treat those diseases, yet neither will likely be considered an ultra-rare disease by ICER.

The National Organization for Rare Disorders (NORD) issued a blistering comment about ICER's limitation of the Framework to diseases with 10,000 patients or fewer.²⁶ Pointing to ICER's claim that a revised methodology should only be used for these smaller populations, NORD wrote, "We find this claim to be baseless and unfounded, and the lack of any outside citation or justification only furthers our conviction. There are many factors that contribute to the difficulty of evidence generation for orphan therapies, and we are confident that they do not start or stop at the 10,000 prevalence number. For example, many diseases with prevalences above 10,000 are even more difficult to develop therapies for due to the heterogeneity of the manifestation, progression, and severity of the diseases, as well as the variability of treatments."

Given the arbitrary nature of ICER's definition of rare diseases, as well as their QALY thresholds, they were likely chosen to cast the widest possible net for their broader and more severe price control regime that is at the heart of the ICER model.

Conclusion

In early 2017, when ICER announced it would make "modifications" to its "value framework" for ultra-rare disease treatments, they were making a huge concession, essentially conceding that their model was failing to capture the value society attaches to therapies to treat rare diseases. In short, their model did not work for rare diseases.

With this announcement, there was hope in the patient advocacy community that ICER might show flexibility when valuing many of the promising rare disease treatments. As the new framework was developed, it became clear however that the patient advocates' hopes were misplaced. Not only would the framework be limited to very small populations, the revised framework was not substantially different from its predecessor. ICER's continuing negative reviews of rare disease drugs seem to indicate that their goal is not to accommodate the unique contextual challenges of rare disease therapies but simply to push their prices down without really considering the value that these treatments bring to patients. Moreover, an argument can be made that ICER increasingly sees its mission as scrutinizing orphan disease drugs. Their rush to issue a negative value assessment of Zolgensma on the very day it was approved by the FDA seems to reflect ICER's inordinate focus

ICER's negative reviews of rare disease drugs suggests that their goal is not to accommodate the unique contextual challenges of these therapies but simply to push their prices down.

on discounting the value of rare disease treatments.

In early 2019, ICER announced yet another project to revise its methodology for rating "potentially curative treatments" such as "gene therapies."²⁷ This project is a further acknowledgment that the ICER model is ill-suited to evaluate cutting-edge treatments emerging from biopharmaceutical laboratories. The constant rethinking of the ICER model should give pause about its "top down" approach to evaluating the value of drug therapies. Just maybe a "bottom up" approach in which patients, their physicians, their caregivers, their health plan and a variety of social actors make judgements about the value of particular therapies for particular patients. This latter approach may not be favored by those economists who want to "control" health care decisions on behalf of others, but it is a system that most Americans tend to favor.

ICER's approach to rare disease drugs is highly troubling for patients with these diseases, for the physicians who treat them, and for the family members or caregivers who help them. Never has the prospect of breakthrough cures for some of the most terrible diseases that plague humankind been stronger. Our knowledge of human chemistry, biology and genetics is increasing exponentially and, finally, that knowledge is beginning to bear fruit in the form of drug approvals based upon this new knowledge.

Why, at this moment in history, would policy makers and payers consciously choose to adopt a cost-effectiveness model that is not only arbitrary, but is particularly ill-suited to evaluate the very therapies that will flow from our explosion in knowledge?

A short time after Zolgensma was approved, Acting FDA Commissioner, Ned Sharpless was interviewed and asked about the costs of gene therapies. Even though the costs of medications are not the FDA's jurisdiction, Sharpless nonetheless expressed frustration at the focus on cost when the scientific progress for patients was so stunning. Of Zolgensma, Sharpless said, "This is a completely novel, almost magical miracle that ends a devastating disease for lots of little kids and the thing you care the most about is the price? I mean, really? If you are so cynical you can't see how wonderful and great this is... you need to re-wear your happy hat."²⁸ Indeed.

Endnotes

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Dr. William Smith is Pioneer's Visiting Fellow in the Life Sciences. Dr. Smith has 25 years of experience in government and in corporate roles. His career includes senior staff positions for the Republican House leadership on Capitol Hill, the White House Office of National Drug Control Policy, and the Massachusetts Governor's office where he served under Governors Weld and Cellucci. He spent ten years at Pfizer Inc as Vice President of Public Affairs and Policy where he was responsible for Pfizer's corporate strategies for the U.S. policy environment. He later served as a consultant to major pharmaceutical, biotechnology and medical device companies. Dr. Smith earned his PhD in political science with distinction at The Catholic University of America.

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