New cost-effectiveness model aims to better capture value of medicines to society

No Patient Left Behind's updated methodology accounts for disease severity, loss of market exclusivity and social value

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September 6, 2023 10:47 PM UTC

A biopharma industry-backed organization, No Patient Left Behind, is advocating for adoption of a methodology for assessing pharmaceutical cost-effectiveness that it believes more accurately captures the value of medicines to society than traditional methods. Acceptance of the methodology, which accounts for disease severity, price declines due to the loss of market exclusivity and the social value that accrues as a drug is used to treat successive cohorts of patients, could help calm the furor over drug pricing and preserve incentives for innovation, according to NPLB.

Published on Sept. 6 by NPLB, a non-profit organization comprising biotech investors, researchers, physicians and patient advocates, the report calls out traditional cost-effectiveness analysis methods such as those used by Institute for Clinical and Economic Review (ICER), for failing to capture “important components of social value.” It illustrates the difference between its proposed approach and ICER’s methodology by recomputing the cost-effectiveness of 20 drugs previously assessed by the Institute.

NPLB was founded by Peter Kolchinsky, managing partner at RA Capital Management, who sits on the non-profit’s steering committee and is a vocal critic of traditional cost-effectiveness models.

Peter Rubin, NPLB’s executive director, told BioCentury that the goal of the report was to “get the math right and improve the accuracy of cost-effectiveness analyses so that payers, patients and innovators all benefit from a more accurate view.”

“We want to make sure folks understand and are educated about the flaws in the current system and how it can be improved.”
Peter Rubin, No Patient Left Behind

He said that the report specifically called out ICER “to add relevance to U.S. readers,” due to the influence the Institute has had over state prescription drug affordability boards (PDABs) and the coverage decisions of private payers. ICER also plans to submit a public report to CMS to inform the agency’s initial round of Medicare price negotiations.

ICER counters that the assumption that cost-effectiveness analyses should weigh health differently depending on the severity of a condition is controversial because it raises questions of fairness, and that part of the reason that drug price declines due to loss of market exclusivity have not traditionally been factored into cost-effectiveness modeling is that the prices typically rise quite a lot before exclusivity is lost.

It also notes that although dozens of new HTA methods are introduced and debated every year, very few become widely accepted.

Getting the math “right”

By accounting for disease severity, price declines from loss of exclusivity, and the social value that accrues as a drug is used to treat new cohorts of patients long after its initial launch, the NPLB report says that 18 out of the sample of 20 drugs are cost-effective. Using traditional cost-effectiveness measures, ICER had found that only eight were cost-effective.

The NPLB report accounts for disease severity using a methodology called generalized risk-adjusted cost-effectiveness (GRACE), which was developed three years ago by Darius Lakdawalla of the University of Southern California and Charles Phelps of the University of Rochester.

Lakdawalla told BioCentury that GRACE captures the idea of diminishing returns in health improvement — a general phenomenon in which people who are less healthy value an improvement in their health more than healthier people.

“It’s just like somebody lives in a huge suburban house values 100 square feet of extra space less than someone who lives in a studio apartment,” he said. “It’s a common idea in economics, but it has not previously been properly incorporated into cost-effectiveness.”
Lakdawalla said that by capturing the idea of diminishing returns, GRACE corrects a long-standing criticism of the cost-effective assessments by health technology assessment (HTA) agencies — that they undervalue treatments for severe illnesses.

Evidence for that claim, he said, includes consumer research, the invention of ad hoc “proportional and absolute shortfall methods” such as U.K.’s Cancer Drugs Fund, and the special treatment accorded to orphan drugs by payers and HTA bodies, including ICER.

Lakdawalla added that “GRACE provides a logically coherent solution by observing that if you simply incorporate this idea of diminishing returns into traditional cost-effectiveness, the idea that people who are sicker value health improvements more just because they’re in worse states, then it actually delivers the implications that we see are consistent with real beliefs.”

Disease severity is incorporated into the GRACE calculation using a “quality-of-life weight” for each indication.

Lakdawalla said that the report also addresses two other purported defects in traditional cost-effectiveness analysis — that it doesn’t account for the decline in drug prices that occurs when patents expire, also known as “dynamic pricing,” and considers only “a single snapshot of the first patients to get a treatment.”

In contrast, the report assumes a drug will drop in price by 76%, 14 years after launch. Lakdawalla said 14 years is the average length of time to loss of exclusivity, and 76% was a “blended average” obtained from studies on the subject. All the products used as examples in the report were small molecules, and it did not specify whether different numbers should be used for biologics.

The report also considers a drug’s “social value” by modeling the benefits reaped not only by the first patients to get treatment, but by subsequent groups of patients as well.

It does this by introducing annual cohorts of new patients into the analysis, meaning that for chronic diseases, the total number of patients on a treatment would rise each year as the model is extended into the future. At the individual level, the clinical benefit of the drug is modeled as the same across all patients, but because there are more of them over time, the total benefit to society increases. The drug price used in the model is also the same across patients, and eventually drops due to loss of exclusivity.

“These ‘stacked cohorts’ reflect the true nature of benefit that any drug can provide,” the report states, adding that “their use is particularly important in diseases with many years of chronic treatment involved, including, for example, multiple sclerosis, sickle cell disease, nonalcoholic steatohepatitis, diabetes, cystic fibrosis, psoriasis, and ulcerative colitis.”

The report states that 60 annual cohorts were used in the analysis, but did not disclose a rationale for that number. Lakdawalla said the exact number of years a drug remains in use isn’t critical to the analysis.

“In principle, you want to follow stacked cohorts forever, because a new drug sets a new standard of care that persists forever,” he said. “Looking at too short a horizon effectively overstates the value of future drugs by attributing the current treatment’s benefits to them.”

**ICER’s Pearson says GRACE is interesting and controversial**

ICER President Steve Pearson told BioCentury he had a “lot of respect” for people working on GRACE, characterizing it as an “important method” worthy of consideration.

However, he added that “there have been no published articles actually using it, much less consensus that it represents a best practice,” and that NPLB’s report “may be the first.”

He then laid out three criticisms of the methodology used in the report, and pointed out risks associated with the overvaluation of drugs.

First, he said the assumption that cost-effectiveness analyses should weigh health differently depending on the severity of a condition “raises questions of fairness, on a population basis, that not everyone is comfortable with.”

“Work on this goes back 30 to 40 years,” he said. “There’s no real consensus on this, and it has not in any way become a standard for health economics.”

He added that the relative risk aversion of a patient population is “one way to measure severity, but not the only way.”

“HTA groups have not tried to quantify this, with very rare exceptions,” he said, adding that ICER uses a formal process that creates a range of cost-effectiveness results, and then considers the different effects of severity, racial disparities and other ethical issues within that range.

He added that some HTA authorities, including those in England, Norway and the Netherlands, have developed different ways of weighting quality in an attempt “to capture severity as a modifier for cost-effectiveness,” but that none of them use GRACE.

“**It’s not like there’s one easy answer out there.**”

*Steve Pearson, ICER*  
Ethical questions raised include the extent to which society should pay a premium for treatments for severe conditions.

“Is that what health insurance is supposed to cover? Should we pay more for that or not? Is that something they could pay for on their own? Does that mean that we should have a higher price for those treatments? I think it’s not unreasonable to say that we should, but it does raise some questions.”

Those questions include whether using GRACE leads to double-counting of health benefits.
“Some people think that it double counts” based on the way health benefits are currently measured, he said. “They think we capture some of what’s in GRACE already.”

Second, he said consideration of dynamic pricing “has not been the norm in the academic literature” because of the number of unknowns it would add to the model.

“Academic health economists have almost never factored in price drops that could occur many years in the future,” he said, adding that it’s hard to know how much a drug’s price will rise before loss of exclusivity, how the prices of comparator drugs will change, how the standard of care for the particular indication will change, and how successful a manufacturer will be at using patents to delay genericization.

He added that even among health economists who believe dynamic pricing is worth trying, “there is no one right, established way to model changing prices.”

Third, he said although stacked cohorts are “one approach” to measuring social value, “there are other ways, and all are still experimental.”

More generally, he said that although GRACE does not always suggest a drug’s price should be higher, that is often the outcome, and the overvaluing of drugs can be harmful, especially in health systems with fixed budgets.

“For every new thing we’re valuing, we have to think ‘What’s the thing that won’t be done because now we don’t have the money for it?’” he said. “What we’re going to lose is even more important from an equity perspective because people of lower incomes and people of color are more likely to have to self-ration care if costs get too high.”

Lakdawalla and Pearson have different views about the best way to frame value discussions. While Pearson characterizes spending decisions as trade-offs within a finite healthcare budget, Lakdawalla views drug spending as an investment that should be assessed based on returns.

“Healthcare spending is an investment problem, not a budget allocation problem,” he said. “Just like any investment problem, you invest until the cost of capital exceeds the rate of return.”

The fact GRACE isn’t used by any HTA bodies isn’t surprising, he added, because it’s only existed for three years.

**NPLB’s analysis of the 20 drugs**

The report presents six different values of incremental cost-effectiveness ratio for each of the 20 drugs previously assessed by ICER — four using GRACE, and two using traditional cost-effectiveness assessment methods.

The GRACE estimates include a “base case” calculation that incorporates dynamic pricing and social value.

Lakdawalla chose the multiple sclerosis (MS) drug Tecfidera dimethyl fumarate from Biogen Inc. (NASDAQ:BIIB) to exemplify the report’s findings.

ICER’s original analysis, he said, led to an incremental cost-effectiveness ratio of $210,000, “which means that for every quality-adjusted life year (QALY) gained, it costs $210,000 to gain that using this drug.”

“ICER would say that’s too much,” he said, adding that the institute’s threshold for cost-effectiveness is $150,000 per quality-adjusted life year gained.

However, using GRACE makes the incremental cost-effectiveness ratio for Tecfidera fall to $52,500 — far below the $150,000 threshold.

That means the price of Tecfidera can be justified, provided the severity of MS and Tecfidera’s genericization and social value are taken into account.

The first generic Tecfidera was approved in 2020, seven years after Tecfidera’s initial FDA approval. Rather than use the seven-year exclusivity number in the model, Lakdawalla argued it’s better to employ the average exclusivity period to cost-effectiveness calculations “since our goal is to demonstrate how generalized [cost-effective assessments] can be used at the time of a drug’s launch” when it is “uncertain how long a drug will maintain exclusivity.”

Of the 20 drugs assessed, the report found that 18 had incremental cost-effectiveness ratios below $150,000 and could therefore be considered cost-effective. ICER previously concluded that only eight were cost-effective.

The report also assessed the value each of the 20 drugs delivers to society versus their respective manufacturers.

“The division of social value is interesting because it tells you who’s benefiting most,” said Lakdawalla. “Is it the innovator, in terms of high drug prices? Or is it the consumer who’s getting a lot more than what they’re paying?”

For Tecfidera, the report concludes the split was 21% to Biogen and 79% to society.

That split, said Lakdawalla, confirms that Tecfidera was reasonably priced, because the value flowing to Biogen in sales was less than the value produced for patients, their families, and society.

Fumarate had been used to treat psoriasis in Europe since the 1950s. With Tecfidera, a second-generation dimethyl fumarate product, Biogen brought a version of the drug with fewer side effects to the MS market. The value to the manufacturer vs. society may split differently for brand new drugs.

Lakdawalla noted that drug companies should not use a finding of a sub-$150,000 cost-effectiveness threshold as an excuse to raise prices.

If they did, he said, that would be like saying “exactly 100% of the social value should go to the drug company. It’s not clear that’s the right strategy for society.”
Other drugs studied in the report include three that were included on CMS’s inaugural list of drugs that will undergo price **negotiation** under the Inflation Reduction Act: Jardiance empagliflozin from Boehringer Ingelheim GmbH, Xarelto rivaroxaban from Johnson & Johnson (NYSE:JNJ) and Januvia sitagliptin from Merck & Co. Inc. (NYSE:MRK). The report found that the incremental cost-effectiveness ratios for each are far below the $150,000 threshold.

The IRA instructs CMS to find the lowest possible “fair” price, which is different from assessing whether prices reflect value to patients and society, the exercise NPLB has undertaken.

**Addressing the QALY controversy**

The NPLB report also states that GRACE resolves another criticism of cost-effectiveness assessments — their reliance on QALYs, which advocates say are discriminatory because they assign more value to a year of perfect health than to a year of compromised health, and thereby underestimate the value of the extra time or quality of life a drug may give to a person living with a disease or disability.

This criticism of QALYs led the federal government to prohibit use of cost-effectiveness assessments by Medicare and certain other federal agencies; the Inflation Reduction Act extended this language, and pending legislation, H.R. 485, would expand the prohibition.

In response, ICER created the Equal Value of Life Years Gained (evLYG) **metric**, which assigns equal weight to gains in healthy life years, regardless of age, disability or illness.

Pearson said the institute had decided to change evLYG “because of some of the concerns around equity in the results.”

In contrast, GRACE says that it’s worth more — not less or even the same amount — to improve the health of disabled people. The method separately considers health-related quality of life (HRQoL) and longevity, rather than relying on QALY as a single index of both.

Lakdawalla said GRACE therefore complies with the IRA, which he said stipulates that value assessment metrics cannot consider life-extension less valuable for the aged, terminally ill or disabled.

ICER’s evLYG should also meet that definition.

Lakdawalla conceded that it is unlikely that CMS would use GRACE when calculating the **Maximum Fair Prices** of drugs under the Act. “What they’ve said is that they’re going to do something qualitative, which is concerning because it just invites discretion, which leads to a lack of predictability and transparency,” he said.

Pearson said ICER would address GRACE in its response to the public comments regarding its value assessment framework, which it expects to publish on Sept. 25, and that the 2023 version of the Institute’s value assessment methods proposes accounting for drug price declines due to the drug pricing provisions of the IRA.

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“Fairness in some ways can be in the eye of the beholder, depending on how broad your view of who’s being affected and where the money goes.”

He concluded, “It’s not like there’s one easy answer out there.”