THE LAST WORD:

Tirzepatide for Type 2 Diabetes
ICER's Final Evidence Report
Issued February 15, 2022

On February 15, 2022, ICER issued a Final Evidence Report on the clinical and cost-effectiveness of tirzepatide, a new insulin treatment for Type 2 diabetes. After following its typical process, ICER concluded tirzepatide works better than some insulin products already on the market. In addition, ICER recommended an annual price range for the treatment, which has not yet been approved by the FDA. Due to the longstanding deficiencies in ICER's modeling framework, the findings in this report – particularly those related to pricing and value – can largely be dismissed out of hand.

Type 2 diabetes (T2D) is a chronic condition characterized by high blood sugar, insulin resistance, and inadequate insulin secretion from the pancreas. Most often occurring in patients over age 45, T2D can result in several life-altering – and potentially life-threatening – complications, including: cardiovascular disease, kidney failure, blindness, lower limb amputations, and cognitive dysfunction. According to the Centers for Disease Control, roughly one in ten – or around 37 million – Americans suffer from T2D.

The most recent estimates (2017) from the American Diabetes Association put the estimated total economic cost for diabetes at $327 billion in the U.S. alone. The largest components of that estimate are hospital inpatient costs and medications to treat complications arising from diabetes, both accounting for roughly 30 percent. Anti-diabetic agents and diabetes supplies produce about 15% of the total costs associated with the disease.

The evidence report considers the value and effectiveness of **tirzepatide,** a novel, weekly injectable sodium glucagon-like peptide-1 receptor agonist (GLP-1 RA), the category of treatments most often selected for patients with high risk of serious complications related to T2D. Eli Lilly – the manufacturer of tirzepatide – submitted a biologics license application with priority review to the Food and Drug Administration (FDA) in October 2021. An approval decision is expected sometime in the summer of 2022.

Clinical Effectiveness

According to ICER, the available data provide a "high certainty" that tirzepatide confers a net health benefit compared the existing standard background therapy. But, when measured against existing therapies in the same class, ICER concluded that it had only comparable or incremental health benefits. ICER attributes much of its conclusion to the beneficial cardiovascular and renal data that exists for the other treatments, but not for tirzepatide.

In a statement accompanying the report, ICER's senior vice president of health economics said that "studies of cardiovascular outcomes with tirzepatide have not been concluded, and therefore there is still uncertainty on its true comparative clinical effectiveness in relation to other available treatment options."

However, the report mostly glosses over the fact that phase three trials for tirzepatide – which will likely produce such data – are ongoing. Therefore, the lack of relevant data is not a reflection of the treatment's clinical effectiveness, but of ICER's timing.

All of this begs the question: Why is ICER performing this analysis now? Why not wait until the data become available? Or, at the very least, why not wait until the FDA decides whether to approve tirzepatide?

Cost Effectiveness

The cost effectiveness analysis in the report suffers from much of the same failings. As always, the section of the final evidence garnering the most attention is the one featuring Health-Benefit Price Benchmarks (HBPB) – estimated price ranges at which ICER claims a drug can be considered cost-effective. Based on the available data – which, once again, ICER acknowledges is insufficient to draw any definitive conclusions – ICER declares that a "fair" price for tirzepatide is somewhere between $5,500 and $5,700 a year.

Another key data point missing from ICER's analysis is the actual price of tirzepatide. Rather than waiting for the manufacturer to set a price, ICER simply assumes the same net price as a T2D treatment already on the market as a placeholder. In other words, ICER claims to have made a rigorous assessment of the cost effectiveness of tirzepatide without knowing what it costs.

Imaginary Models

The fundamental flaws in ICER's modeling removes the report's analysis and conclusions even further from reality. As we've noted many times, ICER's valuation claims are not the result of rigorous analysis. They are based largely on assumptions plucked from literature – often no better than guesswork – rather than long-term clinical data. Their assumptions are then used to populate simulations that capture the hypothetical progress of hypothetical patient populations moving through various disease stages over the course of their hypothetical lifetimes.

All of this means the outcomes produced by ICER's simulations – the basis for its claims about fair pricing – are almost entirely dependent on what assumptions are made up front and which instruments are chosen from the available literature.

In the case of tirzepatide, ICER claims to have modeled the long-term health outcomes for T2D patients in the absence of any long-term data. Moreover, the model selected by ICER, and its expert academic advisors is only one of some 30 models developed to support value claims in diabetes over the past 20 years. If ICER had chosen another framework, the results would likely have been quite different, yet no more or less credible.

Put simply, ICER's modeled claims are imaginary. The simulations that produce them are driven entirely by subjective assumptions. The conclusions produced by ICER's modeling cannot be empirically evaluated or replicated. Thus, they fail to meet even the most basic requirements of scientific inquiry.

The Impossible QALY

The scientific and analytical failures of ICER's methodology have been well documented. On top of the assumption-driven simulations, their models fail to meet the standards for quantitative measurement. Despite widespread criticism, ICER continues to use a "Quality Adjusted Life Year" (QALY) standard to make its cost and value determinations.

Put simply, ICER assigns a monetary value to the quality and duration of a hypothetical patient's life as they move through the simulated stages of a disease. One QALY equals one full year of life in perfect health. The primary purpose of ICER's models – for both clinical and cost effectiveness – is to divine a lifetime incremental cost-per-QALY for any given treatment.

One of many problems with this approach is that the QALY is an impossible mathematical construct. In addition to being driven almost exclusively by assumptions, the scoring algorithms and instruments ICER uses to measure the quality of simulated life produce nothing more than ordinal – rather than ratio – measures. Put simply, this means they can measure whether a patient improved in specified areas, but they cannot measure by how much.

Ignoring the basic standards of fundamental measurement, ICER assumes the instruments they use to measure quality of life – like the EQ-5D-3L-5L, for example – somehow produce mystical ratio measures, even though they were never designed for that purpose.

The ordinal instruments also result in value ranges that do not have a true zero. Without a true zero, the scores cannot be multiplied or divided, which makes them utterly useless in making calculations. Both factors – interval properties and the presence of a true zero – are prerequisites for scientific measurement of response to therapy and change over time.

By utilizing this approach, ICER refuses to acknowledge that, to be credible, value claims must refer to single attributes with ratio or interval measurement properties. They must also be empirically evaluable. This applies to patient-reported outcomes as well as clinical and resource utilization claims. Instead ICER resorts to composite claims that fail all these requirements, which ultimately makes their analysis a meaningless exercise.

In short, the QALY is a mathematical and scientific impossibility that simply cannot be used to make the kinds of assessments ICER attempts in its evidence reports and treatment valuations. Both ICER and its team of academic advisers are aware of these shortcomings to their methodology. Unfortunately, imaginary claims are central to its business model.

If that wasn't bad enough, the QALY also discriminates against patients with conditions like T2D. For those suffering from one of many chronic and incurable illnesses, a year in perfect health is rarely possible. As a result, any valuation based on the QALY will inherently undervalue treatments for those conditions, even if the treatments produce dramatic, improvements to a patient's quality of life.

Conclusion

In its clinical trials, tirzepatide produced positive results for a significant percentage of people with T2D. It may not benefit the entire population, but, so far, the available evidence strongly suggests tirzepatide could provide another treatment option for T2D patients and their clinicians to consider. Overall, tirzepatide is a significant step forward that clinicians and

researchers can hopefully build upon to produce better treatments – and combinations of treatments – in the future.

The most troublesome aspect of ICER's flawed approach is not necessarily the results it produces, but the fact that their imaginary calculations are often used by insurers and public health officials to make coverage decisions for new treatments. In this case, ICER's assessment could very well end up denying many T2D patients access to a new and potentially life-improving treatment. Worst of all, these unfortunate decisions would be based on incomplete information and faulty methods that ignore science in favor of pseudoscience.