PATIENTS RISING NOW

Guide for Commenting on ICER's Draft Evidence Report on Treatments for Type 2 Diabetes

On November 9, 2021, ICER released its draft evidence report, "Tirzepatide for Type 2 Diabetes." This document provides a framework for considering what aspects of tirzepatide – a potential new treatment for diabetes – are important to patients and their families, and how to consider presenting those perspectives. This guide specifically provides insights about how to read and respond to ICER's draft evidence report, as well as how to request a slot to make comments during ICER's public meeting.

Key Dates

November 9, 2021:	Draft Evidence Report released
December 8, 2021:	Written comments due by 5:00pm ET; deadline to submit request to speak at Public Meeting
January 6, 2022:	Updated Evidence Report released
January 20, 2022:	Public Meeting conducted by ICER's New England Comparative Effectiveness Public Advisory Council (CEPAC)
February 15, 2022:	Final Evidence Report and Public Meeting Summary released

Background & How to Participate

The Institute for Clinical and Economic Review (ICER) is a private entity that uses its own analytical process and "value framework" to assess potential new treatments for a variety of diseases. Those assessments often occur before FDA approval, and may result in conclusions that could harm patients by limiting access to new and innovative treatments. You can learn more about ICER here.

There are two primary ways advocates and other stakeholders can give input:

1. **Submit written comments on the draft report, which are due to ICER on December 8th.**
2. **Request a slot to make oral comments during ICER's January 20th meeting.**

Submitting written comments on the draft report

Written comments must be submitted to publiccomments@icer.org as a Word document in 12-point Times New Roman font, and are limited to 5 pages, not including references or appendices. The deadline to submit written comments is 5:00pm ET on December 8, 2021.

Requesting a slot to make oral comments

ICER's public meeting on its revised report and discussion by one of its advisory committees is scheduled for January 20th, and will be held virtually. You can register to watch the meeting here. ICER's meetings have a short period available for public comments. To request a slot to make public comments, an email needs to be sent to publiccomments@icer.org with the person's name, title, and organization. The deadline to make a request to speak is 5:00pm ET on December 8, 2021. Oral comments are limited to no more than five minutes per speaker.

NOTE: Not all requests to make public comments are granted. According to ICER: "We sort through all the requests to make an oral public comment at the meeting. Because we only have a limited time for oral comments at the public meeting, we can only allow a few stakeholders to share their perspective."

Key Points to Consider for Written or Oral Comments

Clinical Effectiveness

- The current ICER review of diabetes is focused on tirzepatide, a potential medicine that is still pending FDA review. The FDA is expected to make a decision on this treatment in the middle of 2022.

- Tirzepatide is a potential new treatment for type 2 diabetes (T2D) that acts in two ways to treat diabetes: One is by acting as a GLP-1 receptor agonist (similar to the existing medicine semaglutide, which comes in both oral and injectable forms); and second by also being an agonist for the glucose-dependent insulinotropic polypeptide (GIP) receptor. This second mechanism of action is a new way to treat diabetes.

- ICER's draft evidence report relied on data from four different trials of tirzepatide, along with other trials of the medicines ICER uses as "comparators" in its modeling – including injectable semaglutide. One of the four trials of tirzepatide directly compares it with injectable semaglutide. Aside from that one trial, as is ICER's normal process, in doing its "analyses," ICER combined data from multiple trials

even though the structure of those trials and the characteristics of the people varied. Those differences raise serious questions about the accuracy and validity of ICER's findings.

- The results of the trials of tirzepatide were very good, with improvements in blood glucose levels and body weight greater than "standard care" as well as compared to semaglutide and empagliflozin, which was the other "comparator" treatment in ICER's modeling. In the research study comparing tirzepatide to semaglutide, tirzepatide improved average blood sugar levels (as measured by HbA1c) by about 2.2% compared to 1.9% for semaglutide, and reduced body weight by about 10kg compared to 5.7kg for semaglutide. And interestingly, while the HbA1c percentages seems to level off by the end of the trial at 40 weeks, weight loss seems to be continuing downward at 40 weeks. (See Figures 1 and 2 below.)

- Tirzepatide was also found to enable a greater percentage of people to achieve both the ADA recommended goal of HbA1c of less than 7.0% (86% v. 79%), as well as "normal" levels of less than 5.7%. (46% for 15 mg of tirzepatide compared to 19% for 1mg of semaglutide among the people in the clinical trial that started with an average HbA1c of over 8.2%). (See Figure 1 below.)

- ICER's major area of criticism of tirzepatide is the lack of cardiovascular outcomes and long-term data. Data for both of those will be coming from ongoing trials. And specific to cardiovascular benefits, ICER's draft report notes:
    - "The SURPASS-CVOT is evaluating the non-inferiority and superiority of once weekly tirzepatide versus dulaglutide (1.5mg) in participants with T2DM and increased cardiovascular risk. The trial has an estimated completion date of October 17, 2024; interim data was unavailable at the time of this report."
    - "In lieu of SURPASS-CVOT data, we sought data on baseline characteristics, efficacy, and adverse event parameters of SURPASS-4, a Phase 3 trial that evaluated three doses of tirzepatide (5, 10, 15 mg) against insulin glargine in adults with T2DM on 1-3 oral antihyperglycemic medications and increased cardiovascular risk. Cardiovascular events were recorded as safety events."

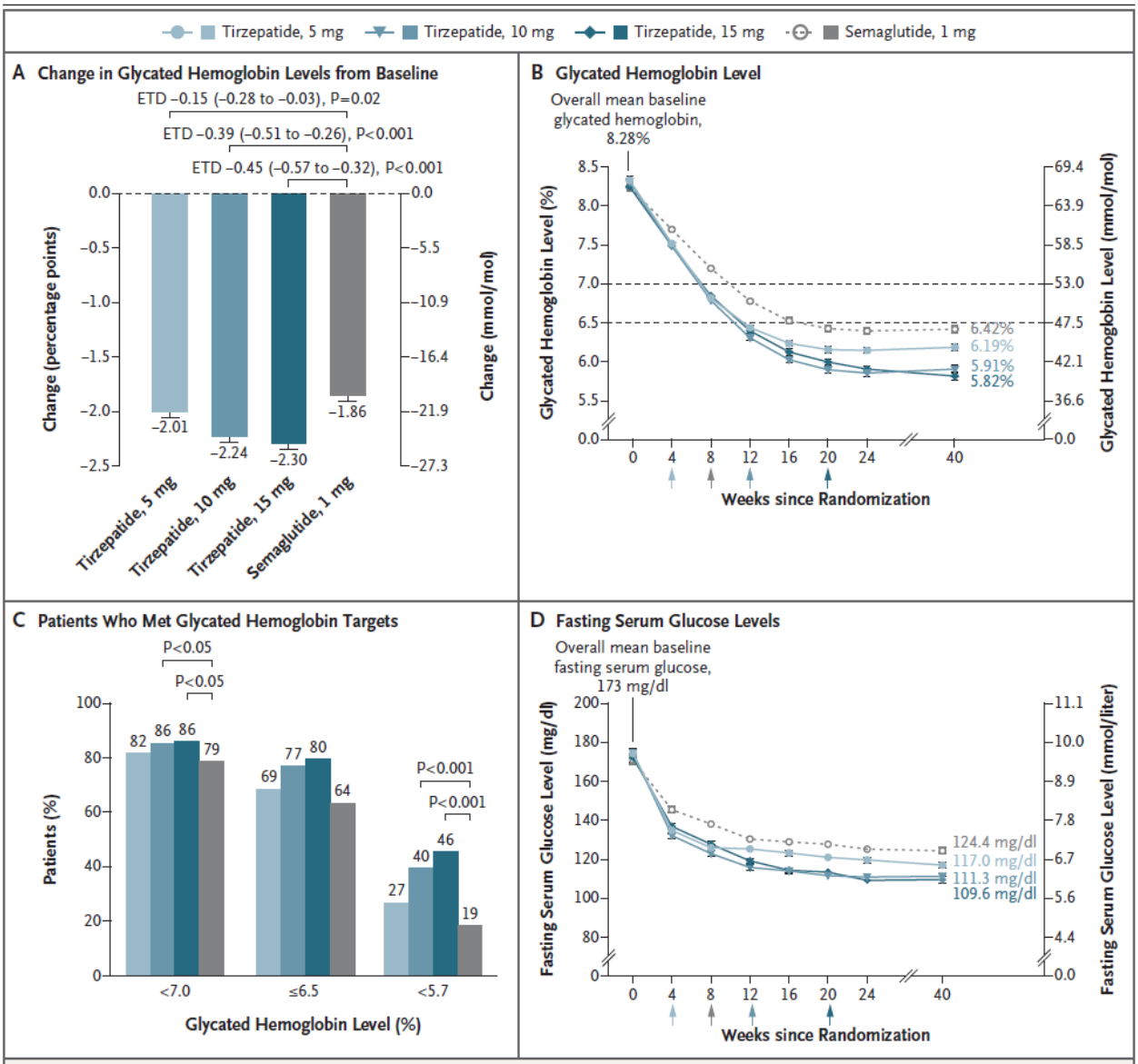

Figure 1. Effect of Once-Weekly Tirzepatide, as Compared with Semaglutide, on the Glycated Hemoglobin Level, Percentage of Patients Who Met Glycated Hemoglobin Level Targets, and Fasting Serum Glucose Levels.

"Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes (SURPASS-2)." The New England Journal of Medicine. 2021;385(6):503-515

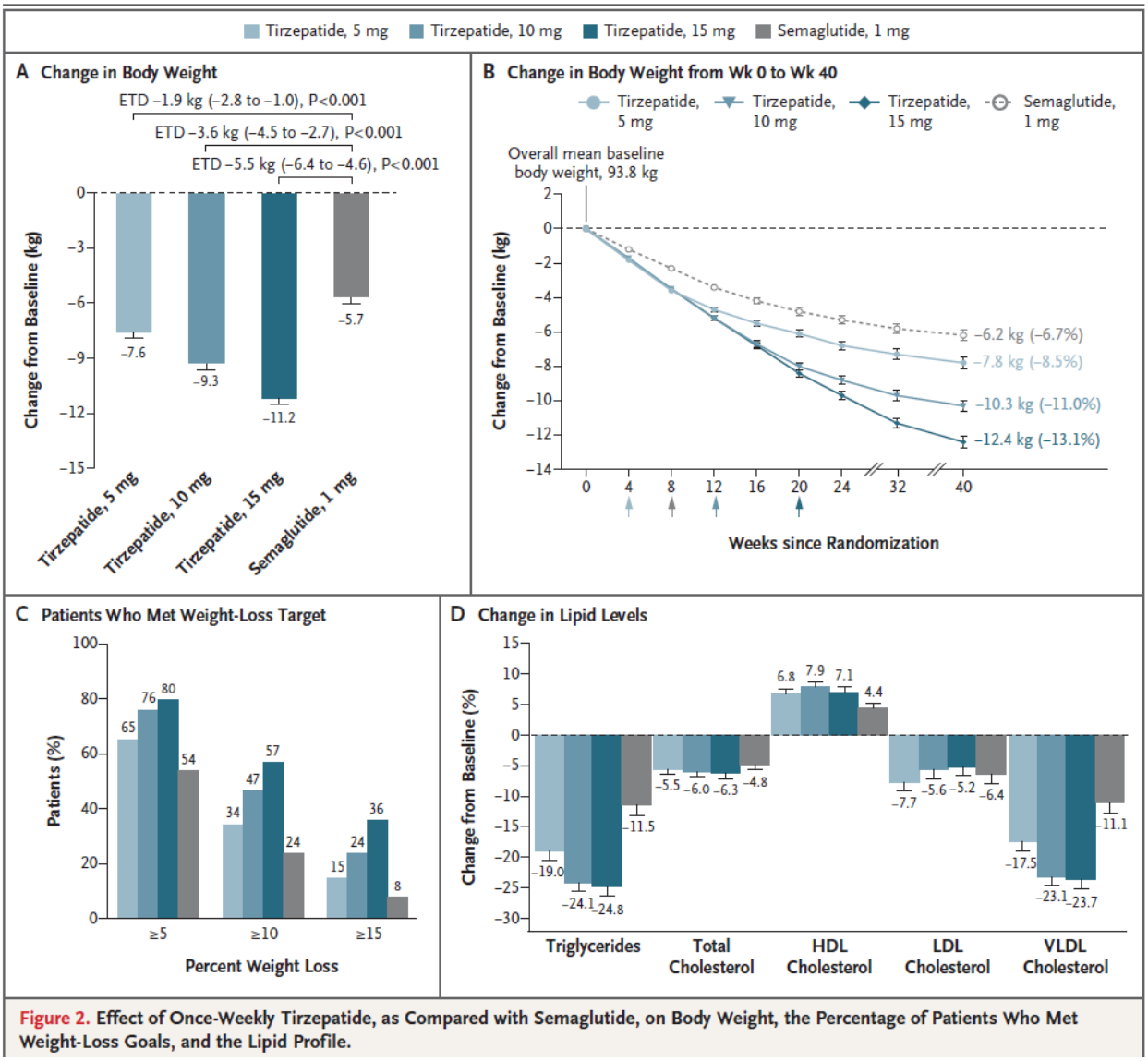

Figure 2. Effect of Once-Weekly Tirzepatide, as Compared with Semaglutide, on Body Weight, the Percentage of Patients Who Met Weight-Loss Goals, and the Lipid Profile.

"Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes (SURPASS-2)." The New England Journal of Medicine. 2021;385(6):503-515

Recommendation: Advocates for better treatments for diabetes should consider making the following points in their written or oral comments:

- Tirzepatide has been found to provide clinical benefits and is superior to semaglutide in improving HbA1c and reducing body weight.

- Provide your personal perspectives and insights as someone with type 2 diabetes (or as a family member or friend of someone with diabetes) about the importance of having more and better treatments – particularly since the expected users of

tirzepatide in the U.S. are going to be the people with diabetes who are not meeting treatment goals using existing medicines, which is almost half of all people with type 2 diabetes in the U.S.

- Discuss how diabetes that is not well controlled with current treatment options affects the daily lives and productivity of people with diabetes and their families.

- ICER notes that cardiovascular and other long-term data will be coming from ongoing studies. ICER should wait until that data is available, or commit to rapidly updating its report when that data is available. Such information will help clinicians and patients understand how to best use tirzepatide in real-world situations, and ICER's work and publications should reflect that goal. At a minimum, ICER should recognize those ongoing trials more directly and specifically in whatever document it produces whenever it is released. Additionally, it is uncertain what the dosing recommendations will be for tirzepatide, so ICER should certainly delay releasing its report until the FDA approves tirzepatide, which will come with the recommended dosage(s) and other important clinical information.

- While tirzepatide will not be needed by every patient with diabetes – nor will it be the treatment solution for everyone with diabetes who isn't currently meeting their goals – it certainly will provide another important option for patients and their clinicians to consider. Joint decision-making by patients and their clinicians about how tirzepatide fits into their individual treatment plan is critical for quality health care that fits the particular situations of specific patients. For example, ICER notes that there are patient preferences for particular injection devices (that are specific to each injectable medicine), which could affect patient adherence to treatments, and ultimately disease control.

Cost Effectiveness

- ICER's economic modeling and analysis has at its core the concept of Quality Adjusted Life Years (QALYs). The use of QALYs for making decisions about payment, coverage, and rationing of care has been widely criticized because QALY calculations assume that people with less than perfect health have diminished quality of life, so QALYs discriminate against people with chronic conditions and disabilities. For example, in the draft report, as part of tits QALY calculations, ICER assigns a health status utility of 0.80 to people with diabetes, compare to 1.0 for someone with "perfect" health.

- Despite the superiority of tirzepatide to semaglutide in an actual head-to-head trial in lowering HbA1c and body weight, in doing its "calculations," ICER's modeling concludes that tirzepatide provides less improvement in Quality Adjusted Life Years (QALYs) compared to semaglutide (4.69 v. 4.76 – see below and table 4.4 in ICER's draft report). It seems that ICER derives this conclusion because of the beneficial cardiovascular and renal data for semaglutide, which does not yet exist for tirzepatide. That is, semaglutide is assumed to provide greater clinical benefits even though it acts via one of the two mechanisms contained within tirzepatide. And interestingly, on page 135 of the 138 page report, ICER concludes that if tirzepatide produces the same cardiovascular and renal benefits as semaglutide, then it would provide superior QALY improvements – and even better cost per QALY gains. (See below.)

Treatment	QALYs	Total Treatment Costs	Cost Per QALY Gained Compared to Background Therapy
Tirzepatide (w/o CV and renal benefits)	4.69	$284,000	$38,000
Tirzepatide (w/ CV and renal benefits comparable to semaglutide)	4.86	$284,000 (assumes no change in treatment costs with CV and renal benefits)	$29,000
Semaglutide (Injectable)	4.76	$289,000	$42,000
Empagliflozin	4.49	$264,000	$2,850
Background Therapy	4.14	$263,000	N/A

Information derived from data presented in ICER's Nov. 9th draft evidence report: Tables 4.4, 4.5 and E.5.

- Thus, it seems ICER has purposefully hidden the relative benefits of tirzepatide by selectively presenting data and comparisons.

- Overall, in doing its analysis, rather than trying to assess each treatment for a disease like diabetes, ICER should assess how ALL treatments for diabetes can improve the health of everyone with diabetes – and that assessment should include interventions like cognitive behavioral therapy (CBT) that can help people improve their diet and increase their exercise, both of which can improve the health of people with diabetes. By taking that approach, ICER would likely find that QALY

improvements from the entire range of treatment options would be significantly greater than what ICER "concludes" by looking at each treatment individually given that every option will not work as well for every patient.

- In developing its economic model for cost effectiveness, ICER makes many wide-ranging assumptions, but ICER does not consider how treatments will improve over time – including the possibility of new treatments that are in development – or how people with certain types of people with diabetes may benefit more from tirzepatide.

Recommendation: Advocates for better treatments for diabetes should consider making the following points in their written or oral comments:

- Question ICER's use of QALYs as a fundamental basis for its cost effectiveness evaluation, particularly because it seems non-sensical to assume zero cardiovascular and renal benefits when one of tirzepatide's mechanisms of action is for the same class as semaglutide, which has been shown to provide those benefits.

- Refute the concept of modeling a "disultility" for someone with a chronic health condition, because everyone has health issues and challenges. ICER designating the "utility" of someone with diabetes as 0.8 is not only methodologically problematic, but also morally questionable.

- While diabetes may be seen by some as a common but not critical health issue, it is important to recognize that not only is diabetes life-altering, but it is the leading cause of blindness, amputations, and kidney failure in the US, and according to CDC data, diabetes is the 7th leading cause of death in the US causing more than 85,000 deaths every year. In addition, diabetes is more prevalent in people of color – who on average have poorer control of their diabetes, which leads to worse clinical outcomes.

- Although there are many types of treatments for diabetes, many, many people with diabetes are not able to achieve a return to normal blood sugar levels, or achieve a normal body weight. While tirzepatide will likely not be a silver bullet, single treatment to achieve that for every patient, as a new type of treatment for diabetes it can significantly help many people with diabetes.

- Insurance companies should not establish very high co-payments, or erect cost-based barriers – such as prior authorization or similar policies – that restrict access

to medicines like tirzepatide. Advocates should raise concerns that by highlighting the lack of certain types of data, ICER's analysis may facilitate insurance companies' establishing higher co-payments and other access barriers for people with poorly controlled diabetes. Such barriers from insurance companies could include difficult authorization forms designed to burden patients and their clinicians in order to prevent patients from obtaining tirzepatide.

Conclusions

- Summarize and restate your thoughts and provide overall recommendations for what ICER should do – or not do – particularly related to the harm that ICER's conclusions could cause by limiting access to this potential new the treatment for diabetes by empowering health insurance companies and government programs to deny payment or create barriers for patients receiving the treatments their physicians recommend.

- Highlight the importance of new treatment options for people with diabetes.

- Question ICER's modeling that "concludes" that tirzepatide – which provides superior improvements in HbA1c and body weight compared to semaglutide – somehow has a lesser effect on QALYs, particularly when the new medicine acts via the same mechanism of action in addition to a novel mechanism for treating diabetes.