October 6, 2025

Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

RE: Draft Evidence Report for Semaglutide and Tirzepatide for Obesity: Effectiveness and Value

Dear ICER,

Boston Scientific Corporation (BSC) appreciates the opportunity to provide comments in response to the Institute for Clinical and Economic Review (ICER) Draft Evidence Report titled *Semaglutide and Tirzepatide for Obesity: Effectiveness and Value*.

Obesity is a complex, multifactorial disease, and existing interventions may not be effective for all adults. Given its high prevalence and significant risk of poor outcomes associated with excess weight, there is a clear need for a broader range of weight loss options. Pharmacological therapies represent an important tool for patients, but with a substantial economic burden to the US healthcare system.

In the background section, ICER acknowledges multiple modalities for treating obesity, including lifestyle modifications, medications, and bariatric surgery. We urge ICER to also recognize endoscopic bariatric and metabolic therapies (EBMT) as an additional option for weight loss. Notably, in its 2026 Patient-Centered Outcomes Research Institute (PCORI) funding announcement, PCORI identified "Addressing Obesity" as a Special Areas of Emphasis (SAEs). As stated in the announcement, *"PCORI is interested in supporting high-quality, patient-centered research to study the comparative clinical effectiveness of intensive lifestyle interventions, anti-obesity medications,* ***endoscopic procedures*** *and bariatric surgery, as well as combination approaches, as appropriate."*[1] PCORI explicitly recognized endoscopic procedures as a distinct category, underscoring their role alongside other established weight loss options.

Many global specialty societies including the American Society for Gastrointestinal Endoscopy (ASGE), European Society for Gastrointestinal Endoscopy (ESGE) and International Federation for the Surgery of Obesity (IFSO), the leading international society for bariatric and metabolic surgeons, have issued guidance on EBMTs for weight loss in patients with obesity.

In conclusion, BSC requests ICER to include **endoscopic bariatric and metabolic therapies (EBMT)** in the description of alternative weight loss procedures**.** Recognizing EBMT aligns with current practice and supports patient-centered care. We appreciate the opportunity to provide this comment and thank you for your consideration.

Sincerely,

Geri Cramer, PhD, MBA, RN
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1. Patient-Centered Outcomes Research Institute. Broad Pragmatic Studies PCORI Funding Announcement -- Cycle 1, 2026. Accessed October 2, 2025. https://www.pcori.org/funding-opportunities/announcement/broad-pragmatic-studies-pcori-funding-announcement-cycle-1-2026

Eli Lilly and Company

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Sent via e-mail to publiccomments@icer.org

October 6, 2025

Institute for Clinical and Economic Review (ICER)
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RE: Comments on ICER's Draft Evidence Report on Treatments for Obesity Management

Eli Lilly and Company (Lilly) welcomes the opportunity to provide written public comments on ICER's draft evidence report (DER) for its review of injectable semaglutide, oral semaglutide, and tirzepatide for obesity management (OM).

For nearly 150 years, Lilly has been developing and delivering safe, effective and accessible medications for people across the world. Today, we're at the forefront of transforming the treatment paradigm for people living with obesity or overweight.

Lilly appreciates the attention that ICER has drawn to the evolving OM treatment landscape, and we agree with this assessment's preliminary findings that tirzepatide is cost-effective and has a well-established safety and clinical efficacy profile in the population of interest. Lilly does, however, have concerns and questions regarding: (1) certain assumptions and choices made by ICER in its clinical effectiveness evaluations and economic analyses; and (2) the methods employed by ICER in the conduct of those evaluations and analyses.

Our comments are organized into two sections: (1) global feedback, which covers broad aspects or features spanning multiple domains in the DER; and (2) localized feedback, which addresses specific components or items in the DER.

Section 1. Global Feeback

Evidence Synthesis Methods

ICER's decision to entirely forgo a network meta-analysis (NMA), which would have integrated direct and indirect evidence from clinical trials of the obesity management medications (OMMs) under review, presents a serious methodological concern. This concern is compounded by ICER's subsequent decisions to: (1) conduct a meta-analysis (MA) for only one intervention of interest (i.e., injectable semaglutide); and (2) devote very little attention in the DER to the head-to-head (H2H) evidence comparing tirzepatide to injectable semaglutide from SURMOUNT-5. Together, these decisions may undermine the balance and validity of this assessment's clinical evaluations, have downstream impacts on its economic analyses, and pose challenges for the appraisal committee during deliberations and voting on comparative effectiveness.

To begin addressing the abovementioned concerns, Lilly recommends that ICER uniformly apply the standard set forth in this assessment's research protocol by conducting an MA to generate pooled estimates of tirzepatide's treatment effect versus lifestyle modification (LSM) using data from SURMOUNT-1 and -3. Results from that MA should, as with injectable semaglutide, be used to inform the following inputs in ICER's cost-effectiveness model (CEM): (1) mean percentage change in body weight (%ΔBW); (2) all-cause discontinuation (ACD); and (3) severe gastrointestinal (GI) adverse events (AEs).

Further, we strongly recommend that ICER revisit its analysis of SURMOUNT-5 to ensure that the trial's findings are adequately reflected in the interim evidence report (IER). In its prior assessments of treatments for type 2 diabetes (T2D) and OM, ICER devoted significant attention to discussing evidence from scope-germane H2H trials (i.e., in-depth review of H2H evidence from SURPASS-2 comparing tirzepatide to injectable semaglutide in the 2022 T2D assessment, in-depth review of H2H evidence from STEP-8 comparing injectable semaglutide to liraglutide in the 2022 OM assessment).[1,2] In the DER for this assessment, however, sufficient attention has not been paid to the totality of H2H evidence from SURMOUNT-5 comparing tirzepatide to injectable semaglutide.[3] Apart from cursory

examinations of reported weight-related outcomes[*] and AEs,[†] SURMOUNT-5 is absent from ICER's quantitative and qualitative evaluation of tirzepatide's clinical benefits. There is zero discussion of data from that trial showing tirzepatide's effect on cardiometabolic parameters or its potential impact on prevention of cardiovascular (CV) events, both of which are central to this assessment, in the DER.[4] Lilly urges ICER to evaluate clinical benefits and harms in the IER by separately addressing: (1) each intervention versus placebo (PBO); and (2) tirzepatide versus semaglutide.

Lilly recognizes that conduct of an NMA comparing the three interventions of interest and their impact on key outcomes would present challenges at this stage in the assessment. Nevertheless, we recommend that ICER explicitly recognize the limitations associated with the absence of NMA results and provide a clear and transparent rationale as to why, despite apparent feasibility, one was not pursued.

Equivalence Assumptions

Transitive assignment of clinical benefits from trials of injectable semaglutide to oral semaglutide is not supported without robust scientific rationale and/or direct comparative evidence supporting such assignment. Without explicit support and justification of its choices and assumptions, ICER's assignment of such benefit is methodologically unsound.

Oral semaglutide has lower and more variable bioavailability, requires higher and more frequent dosing, and results in less predictable systemic exposure compared to injectable semaglutide, all of which can significantly influence clinical outcomes.[5,6,7] Thus, ICER's transitive assignment of clinical benefits from injectable semaglutide to oral semaglutide in this review would be supported only with: (1) a mechanistic justification based on validated pharmacokinetic and pharmacodynamic data; and (2) direct comparative evidence demonstrating dose- and formulation-specific equivalence for the specific outcome(s) and specific population(s) under review. In its DER, ICER provides neither form of support to justify its decisions to: (1) model an increase in the mean %ΔBW from week 64 to week 104 for patients taking oral semaglutide based on the primary endpoint from a two-year trial of injectable semaglutide (i.e., STEP-5);[8] or (2) use a hazard ratio (HR) derived from a prespecified secondary analysis from the cardiovascular outcomes trial (CVOT) of injectable semaglutide (i.e., SELECT)[9] to model the direct impact of oral semaglutide on the risk of developing T2D.

Lilly sees no supported rationale for ICER's choice to model additional weight loss beyond 64 weeks for oral semaglutide. Each semaglutide formulation has been studied independently in OM, and they are not considered interchangeable.[10] While longer-term data (>1 year) on %ΔBW from baseline is available for injectable semaglutide, results from trials examining only that formulation (e.g., STEP-5, SELECT) should not be directly extrapolated to oral semaglutide. Absent justification and/or additional evidence, Lilly strongly recommends that ICER assume in its base case that the absolute difference in mean %ΔBW for oral semaglutide is the same at the year one and year two timepoints in its economic model.

Further, in its 2022 OM report[11] and the revised scoping document for this assessment,[12] ICER notes that, when direct evidence is unavailable for an intervention, best practice is to estimate treatment effects indirectly using validated risk equations. Thus, Lilly recommends that ICER use exponential regression from Edelman et al.[13] to estimate the indirect impact of oral semaglutide on T2D in its base case, consistent with the approach used in its prior OM assessment.

Cardioprotective Benefits and CV Outcomes

Additional direct and indirect evidence supporting tirzepatide's potential cardioprotective benefits and impact on reducing the risk of major adverse cardiovascular events (MACE) has recently been made available.[14,15,16] This evidence could potentially influence results and should be incorporated into ICER's IER.

ICER acknowledges in the foreword of the DER that new and emerging evidence may be released in close proximity to its publication and, as such, data that could potentially influence results may not yet have been incorporated or reflected in the preliminary findings. New evidence from SURPASS-CVOT and SURMOUNT-5 has recently been released and should be fully incorporated into ICER's IER.[17,18]

Detailed results from SURPASS-CVOT were presented on September 18, 2025, and they are now available for ICER's reference.[19] As such, Lilly's pre-specified indirect comparison of matched patient-level data from the REWIND and SURPASS-CVOT[‡20] should be used to inform ICER's base-case input for tirzepatide's direct CV effect in its OM

[*] See the section addressing weight-related outcomes for tirzepatide and Table 3.3, *Key Trial Results Related to Weight Loss Outcomes for Tirzepatide,* in DER (p. 30).
[†] See the section addressing AEs for tirzepatide and Table 3.5, *Harms in Key Trials of Tirzepatide versus Placebo*, in DER (p. 35).
[‡] Based on a pre-specified indirect comparison of matched patient-level data from the REWIND and SURPASS-CVOT studies, tirzepatide was associated with a 28% reduction in the risk of MACE-3 versus a putative placebo (HR: 0.72; 95% CI: 0.55–0.94). Estimates were derived using a Cox proportional hazards model adjusted with stabilized inverse-

CEM (i.e., HR of 0.72). Should ICER wish to retain a modeling scenario that leverages the SELECT HR as a "placeholder" value (i.e., HR of 0.80) for tirzepatide, this should be included only as a scenario analysis (SA), which may take a similar form to the SA from the DER that explored alternative direct diabetic impacts for oral and injectable semaglutide.

A post-hoc analysis from SURMOUNT-5, which found that tirzepatide was associated with a significantly greater reduction in predicted 10-year cardiovascular disease (CVD) risk compared to semaglutide in adults with obesity and without T2D, was recently published.[21] Details from that publication should be reflected in the applicable clinical benefit narratives in ICER's forthcoming IER.

Potential Budget Impact

ICER's use of fixed annual thresholds and non-empirical uptake assumptions in its approach to budget impact modeling remains a significant concern.

By applying a fixed annual budget impact threshold (i.e., $880 million in 2025) and relying on non-empirical uptake assumptions (i.e., 100% of the eligible population at the end of 5 years), ICER is limiting the utility and practical relevance of its analyses. Continued reliance on these methods risks biasing decision-making and could negatively affect patient access. Lilly strongly recommends that ICER reconsider its approach for this and future assessments. At a minimum, we would strongly encourage methodological modifications for reviews involving large eligible populations.

Section 2. Localized Feedback

Clinical Benefits: Weight Loss Outcomes

ICER's decision to focus its clinical evaluation on "unadjusted" and "adjusted" mean %ΔBW from baseline, as opposed to the two reported estimands from the OASIS, STEP and SURMOUNT clinical trials, raises important methodological concerns. The choice to present and leverage observed means (i.e., *unadjusted* values) is highly unusual and may distort stakeholders' perceptions of average treatment effect for the primary endpoint from all of the key OM trials included in this assessment.

ICER appears to be relying on digitized graphs and/or manufacturer-submitted data in its examination of the mean %ΔBW from baseline across key OM trials of injectable semaglutide and oral semaglutide. For injectable semaglutide, ICER presents observed means from each trial's full analysis set (FAS) population during the in-trial observation period at the 68 week visit (STEP-1, -3, -8, -10) and 104 week visit (STEP-5).[§] For oral semaglutide, ICER appears to have followed the same approach to present mean %ΔBW at the 64 week visit (OASIS-4).[**] For tirzepatide, ICER has noted that the observed means from the included SURMOUNT trials' FAS populations are not reported graphically and/or publicly available. As such, no *unadjusted* values of mean %ΔBW are presented in the DER for tirzepatide at the 72 week visit (SURMOUNT-1, -3, -5).[††]

Across all three interventions' key OM trial publications, treatment policy and treatment regimen estimands are used to quantify the average treatment effect in all randomized participants, regardless of adherence or intercurrent events, by imputing missing data using prespecified statistical models. In contrast, the observed means that are graphically reported[‡‡] in the above-referenced STEP and OASIS trials' publications reflect only those participants who had a %ΔBW measurement at a specific visit.[22,23,24,25,26,27] As such, these means, while adherent to the intention-to-treat (ITT) principle, may overestimate or underestimate the average treatment effect when compared to the reported estimands that account for available data across each trial's full duration for the mean %ΔBW endpoint. In the case of semaglutide, it appears as though the observed means presented in the DER overestimate the average treatment effect when compared to the reported treatment policy estimands: on an absolute difference (AD) basis for mean %ΔBW, ICER's MA of STEP-1, -3, and -8 presents an *unadjusted* AD value of -13.1% and an *adjusted* AD value of -12.0% as estimates of injectable semaglutide's treatment effect at 68 weeks, while the *unadjusted* and *adjusted* AD values presented for oral semaglutide at 64 weeks from OASIS-4 are -11.9% and -11.4%, respectively.

Lilly strongly recommends that ICER: (1) highlight the two estimands that each manufacturer leveraged in its key

probability weighting based on the probability of a patient belonging to SURPASS-CVOT given baseline covariates. Not controlled for multiplicity-adjusted type 1 error rate. Page 22 ("Indirect Estimate of Tirzepatide Effect vs. a Putative Placebo Matched Population of REWIND") of the EASD presentation provides more details.

[§] See Table 3.1, *Key Trial Results Related to Weight Loss Outcomes for Injectable Semaglutide*, in DER (pg.12)

[**] See Table 3.2, *Key Trial Results Related to Weight Loss Outcomes for Oral Semaglutide*, in DER (pg. 13)

[††] See Table 3.3, *Key Trial Results Related to Weight Loss Outcomes for Tirzepatide*, in DER (pg. 13)

[‡‡] Refer to the following graphs from each relevant trial's publication: STEP-1 (Figure 1B); STEP-3 (Figure 2A); STEP-5 (Figure 2A); STEP-8 (Figure 2); STEP-10 (Figure 2A); and OASIS-4 (Figure 1A).

publications and regulatory filings[28,29] for this assessment's evidence narratives and tables (i.e., the treatment policy estimand and trial product estimand for both semaglutide formulations, the treatment regimen estimand and efficacy estimand for tirzepatide); and (2) use the reported treatment policy and treatment regimen estimands in its MA for injectable semaglutide and, if pursued, its MA for tirzepatide. Use of *unadjusted* values creates unnecessary complexity and incongruencies, introducing a variable that may impact the comparability, transparency and relevance of ICER's assessment as observed means are not represented in other value assessments, systematic reviews and/or clinical guidelines.

Evidence Ratings

ICER's evidence ratings should reflect the totality of intervention-specific evidence across the outcomes of interest in this assessment's defined scope. Assignment of a "Superior" (A) rating when comparing oral semaglutide to LSM and a "Promising but Inconclusive" (P/I) rating when comparing tirzepatide to injectable semaglutide and oral semaglutide is inappropriate and runs counter to established precedent and ICER's own guidance[30] on application of its Evidence Rating Matrix (ERM).

ICER's evidence ratings are conditioned on two factors: (1) the magnitude of the difference between an intervention and its comparator in net health benefit (i.e., the balance between clinical benefits and risks and/or AEs); and (2) the level of certainty, based on the strength of evidence, of net health benefit. These factors are assessed within the framework of an assessment's "PICOTS" (Population(s), Intervention(s), Comparator(s), Time Horizon(s), Setting(s)).

In assigning P/I ratings when comparing tirzepatide to injectable and oral semaglutide, ICER appears to have focused narrowly on "CV effects" (i.e., impact on the rate of CV events, including nonfatal stroke, nonfatal myocardial infarction, non-fatal stroke and CV death) and, more specifically, the lack of H2H evidence from a CVOT comparing tirzepatide to injectable and oral semaglutide. The population of focus for this review was "adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition, who are actively seeking medical management for weight loss; adults with established diabetes are excluded." The PICOTS-defined outcomes of interest extend far beyond direct CV effect and, based on ICER's own guidance and precedent from prior reviews (e.g., ICER assigned a C+ rating to tirzepatide versus injectable semaglutide in its 2022 T2D review; the lack of H2H evidence on direct CV effects was acknowledged, but the rating ultimately reflected the full PICOTS). Lilly strongly recommends that ICER revisit its P/I ratings in the IER.

The evidence base for tirzepatide is robust and adequately powered, with indirect evidence from publicly available meta-analyses and direct evidence from SURMOUNT-5 showing statistically significant and clinically meaningful superiority to semaglutide in reducing body weight and waist circumference; a recently published post hoc analysis also found that tirzepatide was associated with a greater predicted 10-year CVD risk reduction compared with semaglutide.[31,32,33,34] In consideration of the full PICOTS and tirzepatide's body of evidence in OM, ICER's ERM would suggest a minimum "Incremental or Better" rating (B+) for tirzepatide versus both semaglutide formulations based on point estimate of a small-to-substantial net health benefit while recognizing uncertainty on direct CV effects.[35] To reflect residual uncertainty on CV effects, ICER could consider two distinct ratings: (1) an evidence rating comparing tirzepatide to both semaglutide formulations in the population of focus for this assessment, with consideration of the full PICOTS; and (2) an evidence rating comparing tirzepatide to both semaglutide formulations in a subpopulation of adults with obesity or overweight with established, or at increased risk of developing, CVD. In that subpopulation, tirzepatide would likely command a minimum rating of C++ against semaglutide based on: (1) the factors outlined in our above comments regarding new evidence supporting tirzepatide's potential cardioprotective benefits and CV outcomes and; (2) the fact that there is no evidence to suggest a "small (but nonzero) likelihood of a negative net health benefit" for tirzepatide versus semaglutide, which is required for a P/I rating.

As discussed in Lilly's comments on unsupported equivalence assumptions, it appears as though ICER is deriving some degree of certainty regarding oral semaglutide's clinical benefit from injectable semaglutide's evidence base. Lilly recognizes that a single trial can be enough for a "A" rating, but only when that trial is exceptionally reliable, directly relevant, precise, and supported by other lines of evidence. More commonly, an intervention with only a single scope-germane trial would be deserving of a more conservating rating. Given that ICER explicitly separates magnitude from certainty, ICER's ERM would suggest a B+ rating is most appropriate given a point estimate of moderate-to-large net health benefit, but only moderate, not high, certainty due to the degree of evidence evaluated in the DER (i.e., OASIS-4 only). ICER should justify its rating choice more sufficiently in the IER.

Key Model Inputs: AD in Mean %ΔBW

ICER should reconsider its choice of model inputs to estimate the AD in %ΔBW by year one and year two. The current approach is inconsistent and introduces bias in this review.

As conferred in Lilly's comments regarding ICER's evidence synthesis methods, we strongly recommend that ICER conduct MAs for both injectable semaglutide and tirzepatide; these should be leveraged to derive several key clinical inputs for ICER's CEM (i.e., AD in %ΔBW, ACD, severe GI AEs). We also suggested in our comments regarding weight loss outcomes that ICER use reported treatment policy and treatment regimen estimands, as opposed to *unadjusted* means, in any MAs. Finally, in Lilly's comments regarding unsupported equivalence assumptions we urged ICER not to assign benefit, unless supported and justified in the IER, to oral semaglutide based exclusively on evidence from trials of injectable semaglutide. With those factors in mind, Lilly believes that a level playing field in ICER's economic analyses is largely dependent on whether an MA is conducted for tirzepatide with SURMOUNT-1 and -3.

If ICER chooses not to pursue an MA for tirzepatide, the minimum acceptable path forward is for ICER to: (1) reflect the correct value from the graph[36,§§] that they chose to digitize to estimate the AD %ΔBW by year one (i.e., at 72 weeks); and (2) digitize that same graph to either the 98- or 111-week timepoints to approximate the AD %ΔBW for tirzepatide by year two.

If ICER chooses to conduct the recommended MA and use its outputs in the CEM, it would necessitate that: (1) the reported treatment policy and treatment regimen estimands be used for all interventions, due to the fact that observed means from the SURMOUNT-1 and -3 FAS populations during the in-trial observation period at the 72-week visit are not available; and (2) ICER estimate the AD %ΔBW for tirzepatide by year two, with one potential option being extrapolation of available datapoints from the three-year phase of SURMOUNT-1 at weeks 98 or 111 (see Table 1 in the Appendix for additional details regarding these options).

Incremental Cost-Effectiveness Ratios

ICER's decision to focus its CEA on LSM-only comparisons does not meet the real-world needs of stakeholders, many of whom are assessing choice and making value-based judgments between OMMs, not between OMMs and LSM. The aim of ICER's evidence reports is to inform population-based medical policy and pricing decisions; ignoring OMM-to-OMM cost-effectiveness (CE) comparisons represents a missed opportunity.

Lilly recommends that ICER revisit its decision not to include incremental CE ratios comparing: (1) tirzepatide to injectable semaglutide; (2) tirzepatide to oral semaglutide; and (3) injectable semaglutide to oral semaglutide. We would encourage ICER to carry through the approach from its 2022 OM assessment whereby both OMM-to-LSM and OMM-to-OMM incremental CE ratios were included. Should ICER choose to exclude these from its base-case analysis, they should be included in the IER supplement.

Scenario Analyses

ICER's decision to exclude "Drug X" economic analyses from this assessment reflects a positive development. These types of analyses sow confusion, decrease transparency, and are of little utility to stakeholders.

Lilly applauds ICER's decision not to conduct any "Drug X" scenario analyses in its current OM assessment. As conveyed in filed comments pertaining to this assessment[37] and to ICER's 2022 OM assessment,[38] we believe that modeling economic outcomes for inline or pipeline OMMs using inputs from ongoing or recently completed trials without allowing for end-to-end engagement from manufacturers of those products is highly problematic. Lilly encourages ICER to carry through this decision into future assessments.

Lilly appreciates ICER's consideration of the above comments and we look forward to your responses. Should you have any questions or require additional information, please reach out directly to Sean Grande from Lilly USA.

Sincerely,

Kevin R. Hern

[§§] Refer to Figure 1, Panel B (SURMOUNT-1, 3-year phase) from Jastreboff et al.

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Appendix

Table 1

	Option #1 – Revised Values for Tirzepatide; No Additional Weight Loss After Year One for Oral Semaglutide		**Option #2 –** New MA for Tirzepatide; Reported Estimands for %ΔBW Primary Endpoint vs. Unadjusted Means	
	AD %ΔBW Year 1	AD %ΔBW, Year 2	AD %ΔBW Year 1	AD %ΔBW, Year 2
Injectable semaglutide	-13.1%	-14.0%	-12.0%	-12.6%
Oral semaglutide	-11.9%	-11.9%[1]	-11.4%	-11.4%[1]
Tirzepatide	-19.0%[2]	-19.6%[3]	TBD	TBD

1. AD %ΔBW by year two was assumed to be the same as at year one due to the absence of data beyond 64 weeks.
2. Digitized 72-week value from Figure 1, Panel B in Jastrebroff et al.
3. Digitized 98- and 111-week value from Figure 1, Panel B in Jastrebroff et al.; same value at both timepoints.

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Novo Nordisk Inc. (henceforth referred to as "NNI") is a global healthcare company committed to helping improve the lives of people with obesity by changing how the world sees, prevents, and treats obesity including development of effective medications for chronic weight management. As the manufacturer of Wegovy® (semaglutide) injection 2.4 mg, NNI appreciates the opportunity to provide comments on the *Semaglutide and Tirzepatide for Obesity: Effectiveness and Value Draft Evidence Report*.

As recognized by ICER, obesity is a serious, complex, multifactorial chronic disease that can increase the risk of other diseases including type 2 diabetes mellitus (T2DM), hypertension, liver disease, cancer, obstructive sleep apnea, and cardiovascular (CV) disease.[1] Obesity also incurs a substantial and increasing economic burden to the US healthcare system.[2]

NNI has carefully reviewed the Draft Evidence Report. We are pleased that ICER concluded with a high certainty that injectable semaglutide, oral semaglutide, and tirzepatide were superior to lifestyle modification. We agree with ICER that the evidence shows these interventions result in substantial weight loss and improvements in metabolic risk factors. We are also pleased that the three interventions were found to be cost-effective at well below the threshold of $100,000 per quality-adjusted life year (QALY), when compared with lifestyle modification using net prices.

Nevertheless, NNI would like to request further clarification from ICER regarding several aspects of the report. In particular, NNI has identified concerns related to certain assumptions made for comparative effectiveness, as well as modeling methodologies utilized in the cost-effectiveness and budget impact analyses. These concerns are elaborated upon in the numbered sections that follow.

1. Comparative effectiveness & modeling of CV effects

Initially, ICER used data from both SELECT and SURPASS-CVOT clinical trials to comparatively assess major adverse cardiovascular event (MACE) prevention for injectable semaglutide and tirzepatide, respectively. In contrast, ICER subsequently used the SELECT trial data only in the cost-effectiveness analysis to evaluate the economic benefit associated with MACE prevention for both injectable semaglutide and tirzepatide.

NNI would like to emphasize, that the SELECT trial was conducted in patients with overweight/obesity and established atherosclerotic cardiovascular disease (ASCVD), where a 20% risk reduction for secondary MACE prevention was specifically observed with injectable semaglutide and standard of care compared with placebo and standard of care.[3] NNI strongly disagrees with the SELECT risk estimates being arbitrarily applied to tirzepatide for the cost-effectiveness portion of this report, particularly in the absence of

evidence that indicates a cardioprotective benefit for tirzepatide among those living with overweight/obesity and established ASCVD, without T2DM. NNI would like to further emphasize that employing data from the SURPASS-CVOT trial for tirzepatide may not be suitable for comparative effectiveness in this situation either, given that this trial was conducted among individuals diagnosed with T2DM and did not include a direct comparison with a placebo.[4]

Additionally, for oral semaglutide, ICER used data from the SOUL trial to model MACE prevention, where a 14% risk reduction was observed.[5] NNI would like further clarification on ICER's justification for this, as the SOUL trial was conducted in patients with high-risk T2DM and a lower dose of oral semaglutide was used compared to the dose assessed in the Draft Evidence Report (3 mg starting dose up to 14 mg maintenance dose).[5]

Since ICER published the Draft Evidence Report, data has been presented from the STEER real-world evidence study that compared the potential benefit of semaglutide and tirzepatide for MACE risk reduction in patients with established ASCVD. Compared with tirzepatide, injectable semaglutide demonstrated hazard ratios (HRs) of 0.71 (95% CI, 0.50 to 0.99) for prevention of revised 3-point MACE and 0.78 (95% CI, 0.62 to 0.99) for prevention of revised 5-point MACE*. This difference was even more pronounced when limiting the analyses to patients who remained on treatment, with HRs of 0.43 (95% CI, 0.24 to 0.78) and 0.57 (95% CI, 0.39 to 0.83) for revised 3- and 5-point MACE, respectively.[6]

Although not specific to a weight management population, further evidence that the cardioprotective effects of semaglutide are perhaps molecule-specific does come from data recently presented from the real-world REACH study that compared semaglutide (Ozempic®) with dulaglutide, another glucagon-like peptide-1 receptor agonist (GLP-1 RA), in Medicare recipients with T2DM and CV disease. A 23% reduction in the risk of heart attack, stroke and death was observed with semaglutide versus dulaglutide.[7,8] However, in the SURPASS-CVOT trial, tirzepatide (Mounjaro®) was associated with a non-inferior, non-statistically significant 8% risk reduction of heart attack, stroke, or CV death when similarly compared with dulaglutide in individuals with T2DM and established CV disease.[9]

Recommendation: We urge ICER to carefully consider the existing as well as recently emerging evidence suggesting that the cardioprotective benefits of semaglutide are, to the best of our knowledge, molecule-specific and not solely attributable to weight loss. We also request that ICER reconsider using data from the SOUL trial to assess the efficacy of oral semaglutide (25 mg) in the patient population being assessed.

2. Model assumption that all patients will reach the highest dose of a treatment

In the cost-effectiveness analysis, the weight loss associated with each treatment is determined based on the outcomes observed in trials administering the highest dose of that

* Revised 3-point MACE includes myocardial infarction, stroke, and all-cause mortality. Revised 5-point MACE includes myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization and all-cause mortality

particular treatment. This approach is predicated on the understanding that clinical practice generally aims for the maximum effective dose, unless constrained by tolerability considerations, or the dose that achieves meaningful weight loss if it is lower than the maximum. NNI would like to stress that both semaglutide and tirzepatide offer multiple dosing options, as outlined in their product labels and reflected in clinical practice.[10,11]

There is published real-world evidence indicating that the real-world usage of the maximum 15 mg dose of tirzepatide is substantially lower than the other maintenance doses. NNI recently published the SHAPE real-world study, and observed that in adults with overweight or obesity and no T2DM, only 25.9% reached the 15 mg dose of tirzepatide at 1 year follow-up.[12] In contrast, 83.5% reached the 2.4 mg dose of semaglutide at 1 year follow-up.[12] This is corroborated by two recent retrospective studies of individuals with obesity or overweight and ≥1 obesity-related complication without T2DM. Both reported that the most common dose of tirzepatide used was 5 mg.[13,14] In one study, 33.0% received the 5 mg dose even at the sixth prescription fill whereas only 4.6% actually received the 15 mg dose.[13] In the second study, 37.1% received the 5 mg dose at the fifth prescription fill and only 1.8% received the 15 mg dose.[14]

NNI would also like to highlight that since ICER published the Draft Evidence Report, clinical data for the 7.2 mg dose of semaglutide has been published, a higher dose than the 2.4 mg injectable dose considered in ICER's cost-effectiveness analysis. The STEP UP trial demonstrated that mean change in body weight with semaglutide 7.2 mg plus lifestyle intervention was -18.7% compared with -3.9% with lifestyle intervention alone, a difference of -14.8% (95% CI, -16.2% to -13.4%).[15]

Recommendation: NNI believes that ICER should incorporate all indicated maintenance doses of tirzepatide in its analysis to prevent the potential for misinterpretation regarding its overall efficacy and cost-effectiveness in real-world settings. Additionally, NNI recommends that ICER explore the implications of utilizing efficacy data from the 7.2 mg dose of semaglutide in a scenario analysis, given that this data is publicly accessible and that ICER has assessed the maximum dosage of tirzepatide.

3. Inclusion and assumptions around oral semaglutide

In addition to injectable semaglutide and tirzepatide, ICER also included oral semaglutide in its assessment of clinical and cost-effectiveness. At the time of this ICER review, NNI have yet to make any formal decisions regarding oral semaglutide, including its place in therapy, access and coverage, as well as pricing strategy. In the Draft Evidence Report, the annual net price of oral semaglutide was assumed to be equivalent to injectable semaglutide and data that was presented at Obesity Week in late 2024 was used to model the efficacy of oral semaglutide.[16]

Since ICER published the Draft Evidence Report, clinical data has been published in peer reviewed journals not only for oral semaglutide[17], but notably for another pipeline oral GLP-1 RA, orforglipron.[18] It is important to consider that oral semaglutide and orforglipron convey

the same status in that they are both pipeline GLP-1 RA monotherapy products administered orally, with published clinical data, yet the decision was made by ICER to omit orforglipron from this assessment.

The recent OASIS 4 trial data demonstrated that oral semaglutide 25 mg alongside lifestyle intervention was associated with a mean change in body weight of -13.6%, relative to -2.2% for placebo plus lifestyle intervention, a difference of -11.4% (95% CI, -13.9% to -9.0%).[17] In ATTAIN-1, the highest dose of orforglipron (36 mg) alongside healthy diet and physical activity was associated with a mean change in body weight of -11.2%, relative to -2.1% with placebo plus healthy diet and physical activity, a difference of -9.1% (95% CI, -10.1% to -8.1%).[18]

Recommendation: As oral semaglutide is a pipeline product that has yet to receive Food and Drug Administration (FDA) approval, NNI continues to recommend that ICER should refrain from including oral semaglutide in its review. However, NNI firmly believes that since oral semaglutide was included, other GLP-1 RA products, namely orforglipron, the next oral GLP-1 RA closest to launch following oral semaglutide, should now be evaluated as well.

4. Inclusion of cirrhosis as an endpoint instead of metabolic dysfunction-associated steatohepatitis (MASH)

In the cost-effectiveness analysis, ICER included liver cirrhosis as one of the obesity-related outcomes that were modeled. However, earlier stages of liver fibrosis were not considered. Semaglutide recently received an indication based on the ESSENCE clinical trial for treatment of noncirrhotic MASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults,[11] which can ultimately lead to cirrhosis. Indeed, several studies have demonstrated that MASH incurs a high cost burden in the US;[19-21] therefore, a treatment that promotes steatohepatitis resolution and reduces fibrosis progression has the potential to drive economic value by reducing healthcare costs and improving health outcomes.

Recommendation: NNI highly encourages ICER to reconsider MASH in their evaluation, as its exclusion will likely lead to an underestimation of the clinical and economic benefits that semaglutide affords.

5. Overestimation of patient numbers in budget impact analysis

In the budget impact analysis, ICER assumed all patients who met the indications for weight management in the FDA labels would take semaglutide (injectable and oral) or tirzepatide over 5 years. This includes all individuals in the US with obesity or overweight (plus one weight-related comorbidity), without T2DM. NNI considers this to be an overestimation of the true number of people in the real world who will take these treatments in the next 5 years. Several considerations are likely to impact how patients will access or pay for these drugs and include (but not limited to): (1) indications for use other than weight management (e.g., MACE risk reduction, MASH etc.);[11] (2) potential supply constraints that may limit

utilization over time; (3) barriers to access for those who are commercially insured, which at present, reflects about 55% of the eligible population.[22]

NNI reiterates that the weight management drugs assessed by ICER were highly cost-effective, representing excellent value for money. However, ICER's budget impact analysis found that these drugs are unaffordable due to an analysis that significantly favors treatments that are targeting smaller populations and is biased against people living with prevalent conditions. NNI notes that to meet ICER's budget impact threshold of $880 million, weight management drugs would only be affordable if they cost less than $10 annually ($880 million / 92 million lives).

Going forward, NNI recommends that ICER should consider more equitable methods of assessing affordability based on the prevalence and severity of this condition. Highly cost-effective therapies, like semaglutide, risk being excluded from coverage despite the high unmet need among people living with obesity. This is solely due to the large burden that obesity imposes in the US, while treatments that are not cost-effective but affordable, for example, may end up being covered, simply because they target a smaller population size. This runs contrary to ICER's purpose of seeking to provide evidence-based assessments on the economic value of medications.

In short, NNI believes that ICER's budget impact analysis could lead to restricted access for patients with high prevalence conditions such as obesity and that it appears to justify denying valuable treatment options solely due to patients having a common disease. Indeed, a bias against common diseases could set a precedent that stifles development of innovative medicines for highly prevalent chronic conditions.

Closing statement

NNI appreciates the opportunity to engage with ICER and provide input on the Draft Evidence Report. NNI applauds ICER for demonstrating the cost-effectiveness of injectable semaglutide and oral semaglutide compared with lifestyle modification at well below the $100,000 per QALY threshold and sincerely hope that ICER will consider our comments and recommendations outlined above for further refinement.

We look forward to the ongoing collaboration throughout the review process.

Sincerely,

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October 6, 2025

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Dear Ms. Emond:

Global Liver Institute (GLI) appreciates the opportunity to provide comments on the draft evidence report for treatments for obesity from the Institute for Clinical and Economic Review (ICER).

GLI is a nonprofit organization founded in the belief that liver health must take its place on the global public health agenda commensurate with the prevalence and impact of liver illness. GLI promotes innovation, encourages collaboration, and supports the scaling of optimal approaches to help eradicate liver diseases. Operating globally, GLI is committed to solving the problems that matter to liver patients and equipping advocates to improve the lives of individuals and families impacted by liver disease and co-existing conditions such as obesity.

Obesity and Liver Disease

The prevalence of obesity in the United States has risen in recent years, paralleling rising rates in liver diseases such as metabolic dysfunction-associated steatotic liver disease (MASLD), also known as nonalcoholic fatty liver disease (NAFLD), and its advanced form, metabolic dysfunction-associated steatohepatitis (MASH), also known as nonalcoholic steatohepatitis (NASH). These diseases

negatively impact our nation's health and economy. The financial burden of obesity is exacerbated by the costs associated with MASH/NASH, including inpatient and outpatient care, professional services, emergency department visits, and drug costs.[1] These diseases also drive indirect costs, such as lost work productivity and expenses due to caregiving.[2] By 2039, it is predicted that healthcare cost per patient due to MASH/NASH will almost double, most likely driven by the growing number of patients with MASH and advanced fibrosis. Costs are higher for patients with obesity and MASH/NASH.[3]

ICER's model must look at liver impacts beyond just cirrhosis

GLI appreciates that ICER included liver-related outcomes in its model but believes these outcomes were too narrowly defined. ICER's assessment incorporates cirrhosis as a patient-important outcome but only includes MASH/NASH as a surrogate endpoint. It is well known in the literature that MASH/NASH impacts clinical outcomes of patients with obesity. Addressing MASH/NASH by promoting steatohepatitis resolution and reducing fibrosis progression in patients before it advances to cirrhosis will both lead to better outcomes for patients and less cost to the system. FDA has approved semaglutide for MASH, and the American Association for the Study of Liver Disease (AASLD) guidelines recommend semaglutide for treatment of MASH, also recognizing its cardiovascular benefits for patients with obesity/overweight.[4] Patients with non-cirrhotic NASH with subsequent progression to a more severe disease state are estimated to have 1.6 times higher follow-up spending than non-progressors, indicating that treatment preventing progression has a significant impact on financial burden for patients.[5] In order to better capture the benefits of treatments for obesity, GLI would encourage ICER to account for the benefits of treating MASH in its model.

ICER Fails to Differentiate Treatments

Patients will respond differently to the same treatments. They have different characteristics, biology, and treatment goals that will mean a treatment that is optimal for one patient will not be optimal for a different patient. In reviewing the ICER draft report, we are very concerned that it does not clarify how the two treatments assessed may differ in providing value to patients. Too often, health economics models assume that each patient is the average and that treatments are one-size-fits-all. In our experience with patients using medications indicated for obesity and

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related conditions, they will report that one treatment provides them with a desired outcome with fewer side effects compared to others. We are very concerned that ICER's final report may be used by payers to force patients into a treatment protocol that does not optimize their outcomes.

ICER's artificial budget cap threatens to limit needed access for patients

ICER correctly finds treatments for obesity to be beneficial to patients and cost-effective. That being said, ICER uses its artificial budget threshold to assume that only 1% of eligible patients could be treated. ICER's use of a budget threshold that inherently devalues treatments for large populations is problematic. The United States is not like foreign countries operating in a single payer market that embraces health care rationing. It is inappropriate for ICER to artificially impose a budget threshold that supports an unnecessary — and un-American — health care rationing scheme that payers may use to limit patient access to needed treatments.

ICER's use of finite fiscal thresholds in assessing budget impact biases its assessments against any intervention for a common condition, regardless of the severity of the condition or the cost-effectiveness of the intervention. It also ignores the compelling studies and real-world experiences indicating that access to obesity medications reduce other health system costs.[6] It would be more efficient to tackle population health problems by empowering solutions that work for large populations — not to penalize health care with expansive potential patient populations that would benefit. The precedent for this direction would be contrary to American efforts to prevent and reduce chronic disease. Therefore, we have significant concerns that ICER's final report will be used by payers to justify reduced access to care through restrictive coverage decisions.

QALYs are discriminatory and should not be used in value assessment

Multiple studies have shown that cost-effectiveness models relying on the quality-adjusted life year (QALY) discriminate against patients with chronic conditions[7] and people with disabilities.[8] There is widespread recognition that the use of the QALY is discriminatory. The QALY has historically been opposed by the American public and policy makers. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.[9]

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[6] Rika Kanaoka, "Lifetime Social Returns from Expanding Access to Anti-Obesity Medications," USC Schaeffer, March 2025, https://schaeffer.usc.edu/research/lifetime-social-returns-from-expanding-access-to-anti-obesity-medications/.

[7] Mike Paulden, "Recent Amendments to Nice's Value-Based Assessment of Health Technologies: Implicitly Inequitable?," *Expert Review of Pharmacoeconomics & Outcomes Research* 17, no. 3 (May 4, 2017): 239–42, https://doi.org/10.1080/14737167.2017.1330152.

[8] Erik Nord et al., "Incorporating Societal Concerns for Fairness in Numerical Valuations of Health Programmes," *Health Economics* 8, no. 1 (February 1999): 25–39, https://doi.org/10.1002/(sici)1099-1050(199902)8:1<25::aid-hec398>3.0.co;2-h.

[9] "National Council on Disability: Quality-Adjusted Life Years and the Devaluation of Life with a Disability," National Council on Disability | Quality-Adjusted Life Years and the Devaluation of Life with a Disability, November 6, 2019, https://www.ncd.gov/report/quality-adjusted-life-years-and-the-devaluation-of-life-with-a-disability/.

Conclusion

GLI urges ICER to review some of its modeling decisions and to ensure it is capturing the full impact of these treatments by considering the impact on MASH/NASH.

Sincerely,

Larry R. Holden
President & Chief Executive Officer
Global Liver Institute

About Global Liver Institute

Global Liver Institute (GLI) is a 501(c)3 nonprofit organization founded in the belief that liver health must take its place on the global public health agenda commensurate with the prevalence and impact of liver illness. GLI promotes innovation, encourages collaboration, and supports the scaling of optimal approaches to help eradicate liver diseases. Operating globally, GLI is committed to solving the problems that matter to liver patients and equipping advocates to improve the lives of individuals and families impacted by liver disease. GLI holds Platinum Transparency with Candid/GuideStar, is a member of the National Health Council and NORD, and serves as a Healthy People 2030 Champion. Follow GLI on Facebook, Instagram, LinkedIn, and YouTube or visit www.globalliver.org.

October 6, 2025

Institute for Clinical and Economic Review
14 Beacon Street, Suite 801
Boston, MA 02108
publiccomments@icer.org

SUBJECT: Comment Letter on the Draft Evidence Report on Treatments for Obesity

Dear ICER Evidence Report Team,

The MAPRx Coalition (MAPRx) appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on Treatments for Obesity. We recognize and value ICER's efforts to assess the clinical effectiveness and economic value of anti-obesity medications (AOMs), a process that is critical for informing coverage decisions across the U.S. healthcare system.

MAPRx, is a national coalition of beneficiary, caregiver, and healthcare professional organizations committed to improving access to prescription medications in Medicare Part D and safeguarding the well-being of Medicare beneficiaries with chronic diseases and disabilities.

We wish to emphasize our strong support for the recognition of obesity as a chronic, life-threatening disease, not merely a lifestyle condition. As a major risk factor for a broad range of devastating chronic disease including diabetes, hypertension, cardiovascular disease, and several cancers—obesity constitutes a public health epidemic. This condition has adverse impacts on the overall health of beneficiaries, including the approximately 40% of U.S. adults aged 65 and over who are living with obesity.[1]

Anti-obesity medications are a critical, evidence-based component of the continuum of obesity care. They are vital for managing this severe, chronic disease and have been shown to help reduce overall morbidity and mortality, often achieving benefits that extend beyond weight loss alone.

The Need for Equitable Coverage in Medicare Part D

While we commend the focus of this ICER report, we must concurrently express our disappointment that the Medicare Part D program remains an outlier among payers. Medicare

[1] Mather, M., & Scommegna, P. (2022). *Rising obesity in an aging America: Policy and program implications*. (Today's Research on Aging, No. 42). Population Reference Bureau. https://www.prb.org/resources/tra-rising-obesity-in-an-aging-america/

Part D's current statutory coverage exclusion of AOMs prevents a significant, vulnerable population—older Americans and those with disabilities—from accessing necessary, Food and Drug Administration-approved, and clinically effective therapies. This exclusion stands in contrast to the coverage policies of other major federal health programs and many state Medicaid plans, which increasingly recognize the critical role AOMs play in improving health outcomes, reducing disease progression, and promoting health equity. Our white paper, "Clinical Evidence Driving Patient Access in Medicare Part D" summarized the health threat posed by the prevalence of obesity and the need for Medicare to update its coverage policy.[2]

We sincerely hope that ICER's final evidence report will robustly highlight the compelling clinical data and economic value of these treatments. The findings from this assessment are paramount, as they can serve as crucial evidence to motivate policymakers, including the Centers for Medicare & Medicaid Services (CMS) and Congress, to rectify the long-overdue exclusion of AOMs from Medicare Part D.

It is our belief that by thoroughly evaluating the full spectrum of patient and population value, including the long-term impact on comorbidities and associated healthcare cost, ICER can provide the necessary clarity to ensure more equitable coverage for all, particularly for Medicare Part D beneficiaries who are currently denied access to this essential care.

Thank you again for undertaking this important analysis and for considering our perspective. We look forward to reviewing the final evidence report. For questions related to MAPRx or the above comments, please contact Bonnie Hogue Duffy, Convener, MAPRx Coalition, at (202) 540-1070 or bduffy@nvgllc.com.

Sincerely,

MAPRx Coalition

[2] MAPRx. (2022). *Clinical Evidence Driving Patient Access in Medicare Part D*. https://maprx.info/new-maprx-report-examines-the-exclusion-of-anti-obesity-medications-in-medicared-partd/

October 6, 2025

ICER
Attn: Sarah Emond
14 Beacon Street, Suite 800
Boston, MA 02108
Dear Ms Emond,

As Chair of the National Board of Directors of the Obesity Action Coalition, I welcome ICER's Effectiveness and Value report, on semaglutide and tirzepatide, that acknowledges meaningful health benefits beyond weight loss, including improvements in cardiovascular health, mobility and quality of life. These innovations offer hope to individuals who have long struggled against weight stigma and limited treatment options. Patients report that these medicines enable them to improve their health and participate more fully in family and work life.

Despite these benefits, access to the medications remains the greatest challenge. Many patients are excluded from treatment due to lack of insurance coverage, restrictive exclusion policies or prohibitive out-of-pocket costs. These barriers to obesity care perpetuate health inequities, particularly for women, people of color, and lower-income communities who are disproportionately affected by obesity. I urge ICER to underscore the importance of fair coverage and affordability in its final report. Recognizing obesity as a chronic disease and ensuring equitable access to these therapies will not only improve individual lives but also reduce long-term health system costs by preventing downstream medical complications.

I agree with ICER's finding of treatments for obesity to be both beneficial to patients and cost-effective. However, there are limitations with the affordability assessment method that concluded only 1% of eligible patients could be treated. This framework is not ideal for therapies taken by large patient populations. The approach ignores evidence that broader access to obesity medications reduces downstream health system costs. I fear that it could penalize patients from getting access to the innovations, where this precedent could be used by payers to justify exclusionary coverage policies. More context and clarity is needed.

I applaud ICER for including patient perspectives as a central part of this assessment process. Including lived experiences of people with obesity helps ensure that evaluations reflect not only clinical and economic outcomes, but also the real-world impact on daily life, dignity, and equity. I encourage ICER to continue prioritizing patient voices and provide context for the affordability assessment as it finalizes this report and formulates recommendations that will shape access to these safe and effective innovations.

Sincerely,
Nikki Massie
Obesity Action Coalition
National Board Chair

Dear Sirs/Madams,

I am submitting a comment regarding the estimated net prices for injectable semaglutide and injectable tirzepatide for the DRAFT Evidence Report "Semaglutide and Tirzepatide for Obesity: Effectiveness and Value" published September 9, 2025.

In the executive summary it is noted that estimated net prices from SSR Health were used in the cost-effectiveness analysis. Specifically, $6,830 for injectable semaglutide and $7,973 for injectable tirzepatide.

As a pharmacist who is employed in a regional, not for profit, payer organization, I can attest that these net prices are not available to us. I have read other information and blogs from others which would suggest that this is a similar theme across payers. If a payer is getting rebates for these drugs, the net prices are still substantially higher than those apparently used in the cost-effectiveness analyses. If a payer is not getting rebates, the prices used are up to two-fold higher than those figures.

Without understanding how SSR Health obtains commercial rebate data to provide estimated net pricing, one concern is that 340B prices, health system GPO prices, manufacturer discounts to wholesalers, and/or Medicaid Drug Rebates could be included which would markedly dilute the overall net prices and such prices are not available to commercial payers.

Importantly, the diabetic versions of semaglutide and tirzepatide have lower WACs and are more heavily rebated that the obesity management versions. Is it possible that the net prices of the diabetes agents were conflated with the obesity versions?

Injectable semaglutide and tirzepatide are both administered weekly and both are dispensed as a pack of four pens equaling a 28 day supply. For a full year supply, that would require 13 packs of four pens. It is a common oversight to multiply a per prescription drug price by 12 when it should be 13 to correctly calculate the annual expense when the drug is a 28 day supply.

It is important that the costs used in the analyses reflect real world circumstances and the net prices (particularly for semaglutide) warrant adjustment in the final evidence report.

Thank you for your consideration,

Laurie L. Lincoln, Pharm.D., BCPS

SVP, Pharmaceutical Care Programs

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1. BMI
    1. I understand that your rationale for using a baseline BMI of 37 is that this is who is currently using the drug. This would be a break from the usual approach to CEAs – I couldn't have modeled PCSK9is by restricting the base case to a substantially higher risk population than those eligible for the drug. Have you used this approach in other models? A quick analysis of NHANES suggests a lower BMI in the treatment-eligible population (In the 2017-2020 and 2021-2023 combined cycles, there are 106.8 million people who meet eligibility criteria for weight management and do NOT have DMl; the mean BMI for these people is 33.34 kg/m2). Cost-effectiveness among current users is a different question, but given rapidly increasing use, not a super interesting one. I still think the starting BMI should be 33; 37 should be a secondary analysis.
    2. But if you assume the question of interest is among current users, then the effectiveness estimate must also be among current users. In my opinion, the best real-world estimate of weight-loss comes from the Truveta analysis (there may be others): https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2821080
    In that model, weight loss is approx. 8.3% for semaglutide and 15.3% for tirzepatide at 12 mo. So the weighted change would be ~11-12%.
    Using baseline BMI from the real-world and %BMI change from the trial (17%) feels like stacking the cards in favor of GLP1s. My base case would be treatment-eligible (BMI 33) and real-world reduction in weight.
    1. The QoL assumptions again very strong (I believe you are assuming -0.01 for every unit increase in BMI, even after the effects of CVD, CKD, DM, OSA without or with excessive daytime sleepiness are taken out and modeled *multiplicatively*). The model is basically saying that going from a BMI of 30 to a BMI of 37 is a lot worse than having a stroke (after accounting for the side effects of weight gain).

2. Re- diabetes,
    1. The effect size and the costs appear reasonable.
    2. Found the QoL assumption large given that you are accounting for CVD and CKD separately (and multiplicatively) – there feels to be some double-counting here, but I may be wrong.
    3. I didn't check whether you have a ceiling with age - incident diabetes tends to level off at 65.

3. Re – OSA: This is another one I struggled with. The model assumes a nearly 40% prevalence at baseline. At age 65 years in the model, prevalence is 37% in the control arm and 21% in the treatment arm (16pp difference, which is enormous). A third are assumed to have excessive day time sleepiness, which the model assumes carries a qol penalty equivalent to living with a stroke. While I agree OSA is important, these assumptions feel unreasonable. At the very least reduce the qol penalty here to 0.02 or 0.03. My sense is that you are double-counting the qoL penalty of OSA and BMI, which would be expected for a condition that is this prevalent. Unless you have very strong data otherwise, I would back-calculate the OSA penalty out of the BMI penalty (and apply to both the baseline and during follow-up).

4. While this is a small driver of costs, my intuition is that some of your annual costs of CVD are too high. For instance, it's hard to imagine that "other CVD (besides MI, stroke, HF?)" incurs 10K per year on average across a 46 yo population. This is important because half the incident CVD events are in this other category I believe.

5. Other issues:

1. I didn't get to ESRD, cirrhosis, etc, though I suspect they are not the key drivers here (could check by setting to zero; I'm sure you did this already).
2. I also didn't look at your assumptions regarding discontinuation (any sustained benefits from prior GLP-1RA treatment? I would assume none). In prior work, the model was sensitive to the duration and magnitude of any benefits that were sustained after discontinuation (as you would expect for a treatment with a lot of discontinuation). It leads to unreasonable conclusions about therapy duration (treating for 1 year and stopping can have the lowest ICERs).
3. On an unrelated note, why is the baseline qol of 46 yo with obesity and no dm 0.85 (separate from the BMI effect?)

When I run a scenario analysis where I adjust the input parameters to what I think is more reasonable, I end up with an ICER of approx. 100-120/QALY which I find credible. That is still somewhat lower than I expected (150-170 based on prior work), but I don't know what else I could be missing, and instincts can definitely could be incorrect!

There seems to be a disconnect between how sick this population appears at baseline and their observed mortality. I suspect this is further depressing the ICER.

Dhruv S. Kazi, MD, MSc, MS
Associate Director and Section Head for Health Economics, Richard A. and Susan F. Smith Center for Outcomes Research
Director, Cardiac Critical Care Unit, Beth Israel Deaconess Medical Center
Associate Professor of Medicine, Harvard Medical School
Associate Professor of Epidemiology, Harvard T.H Chan School of Public Health

To the Institute for Clinical and Economic Review:

This letter pertains to the Draft Evidence Report[1] published by ICER on September 9, 2025 titled "Semaglutide and Tirzepatide for Obesity: Effectiveness and Value."

As physicians and pharmacists that advise formulary management for self-insured employers, we are grateful for the important work ICER does to evaluate the cost-effectiveness of medications. Nowhere is this type of rigorous evaluation more urgent than in the GLP-1 receptor agonist class, and we applaud ICER for their work on this.

We were disappointed to see that liraglutide was excluded from this analysis. The extraordinary cost of these new anti-obesity medications at a population level – laid bare by the budgetary impact projected in section 7 – makes it critically important to understand not only the cost-effectiveness of each agent relative to commonly used thresholds, but also each agent's cost-effectiveness relative to other agents in its class. For a drug class where expense is such a tremendous burden for payers and patients, the exclusion of the one agent in this class that is available as a generic is notable, representing what we view as a missed opportunity.

The FDA has approved generic versions of liraglutide both for diabetes (generic Victoza) and obesity (generic Saxenda). While liraglutide drives less weight loss than semaglutide or tirzepatide, its efficacy has been proven in many trials (including the LEAD series and LEADER trial for diabetes and cardiovascular risk reduction and the SCALE series for obesity), earning liraglutide FDA labeling for weight management in adults and adolescents as well as for glycemic control and cardiovascular risk reduction in diabetes.

Recognizing its importance in the treatment landscape, ICER appropriately included liraglutide in its 2022 evidence report.[2] That report systematically surveyed the literature on liraglutide, semaglutide, and other drugs to establish their cost-effectiveness. However, the price of these agents has decreased precipitously since that analysis was performed. In that 2022 report, the net cost of liraglutide was estimated at $11,000-12,000 annually and semaglutide was estimated at $13,000-14,000.

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[1] Lin GA, Lee W, Fahim SM, Richardson M, Phillips M, Raymond F, Rind DM. Semaglutide and Tirzepatide for Obesity: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, September 9, 2025.

[2] Atlas SJ, Kim K, Beinfeld M, Lancaster V, Nhan E, Lien PW, Shah K, Touchette DR, Moradi A, Rind DM, Pearson SD, Beaudoin, FL. Medications for Obesity Management: Effectiveness and Value; Final Evidence Report. Institute for Clinical and Economic Review, October 20, 2022.

While ICER acknowledges in its 2025 report that the annual net price of semaglutide has reduced to $6,000-7,000 – which dramatically changed the estimate of its cost-effectiveness compared to the 2022 report – the exclusion of liraglutide means that its increased cost-effectiveness by virtue of price reductions is not captured. This is an important omission because liraglutide has not only experienced list price deflation as the other agents in this class have in recent years, but it has also lost its exclusivity and is now available as a generic, which has significant ramifications for the price paid by payers, patients, and the public for this drug.

In its April 2025 report[3] on obesity medications, ICER noted that the annual net price of liraglutide (Saxenda) was $9191, compared to semaglutide (Wegovy) at $7401 and tirzepatide (Zepbound) at $8700. If these figures held true today, it might be reasonable to focus the analysis on the latter two agents and exclude the former. However, since that report, Saxenda is now available as a generic, which impacts its net price in multiple ways. First, the list price of generic Saxenda is lower than its branded counterpart, and due to loss of exclusivity, it is possible that competition may further drive down prices for liraglutide. Second, for generic drugs, the true amount paid by a plan sponsor (a health plan or an employer group) is significantly lower than its list price, because generic drug prices are reconciled at much lower effective rates (as a percentage of average wholesale price) than branded drugs in contracts between plan sponsors, pharmacy benefit managers, and pharmacy networks. Together, these two forces drive significant discounts, making liraglutide a far more affordable option for patients and our health care system overall. We have observed this deflationary process occur in the diabetic indication for these agents, where generic Victoza costs self-insured employers and their members (employees and dependents) a small fraction of Ozempic or Mounjaro.

Given this experience, we expect that the cost-effectiveness of liraglutide in today's environment will be far greater than was estimated in the 2022 report. In fact, it may even meet or exceed cost-effectiveness thresholds, and do so by a greater margin than semaglutide or tirzepatide. Take for example the QALY-based threshold analyses in Table 4.11 of the 2022 report (page 54). There, ICER estimated that the annualized net price to achieve a benchmark of $100,000 per QALY gained was $7500 for semaglutide and $3800 for liraglutide. While semaglutide's current annual net cost (accounting for rebates) according to ICER's estimates is quite close to its threshold value, generic liraglutide's net annual cost today (accounting for its reconciliation as a generic in pharmaceutical purchasing contracts) is far below its threshold and may even be getting lower (as competition grows).

While efficacy does vary between these agents, so does the cost. Liraglutide drives statistically significant and clinically meaningful reductions in weight (as well as HbA1c and cardiovascular outcomes); that these benefits are less in magnitude than the corresponding markers for semaglutide or tirzepatide would only comprise grounds for its exclusion from a cost-

[3] Pearson SD, Whaley CM, Emond SK. Affordable Access to GLP-1 Obesity Medications: Strategies to Guide Market Action and Policy Solutions. Institute for Clinical and Economic Review, April 9, 2025.

effectiveness analysis if the net prices of these agents were comparable. They are not. When viewed from a value-oriented perspective, it is essential to understand whether the incremental weight loss associated with semaglutide or tirzepatide relative to liraglutide is "worth" the additional money spent on those newer, more expensive agents. Whether the differences in efficacy are justified by their differences in cost is an empirical question that can only be answered through rigorous analysis of the type that ICER is known for.

Some might argue that liraglutide need not be considered in an analysis like this because, as the April 2025 ICER report stated, clinical interest is greater in semaglutide and tirzepatide than in liraglutide because liraglutide produces less weight loss and requires daily injections (page 8). In contrast, we believe liraglutide remains an important option in today's pharmacologic toolkit to treat obesity for several reasons:

- **Affordability**: By virtue of now being available as a generic, liraglutide is far more affordable than its peers and has a similar mechanism of action to semaglutide, while earning similar FDA indications for weight management, diabetes, and cardiovascular risk reduction. Not only is this important for payers seeking to manage budgets under increased financial pressure, but greater drug affordability also reduces premium growth and out-of-pocket expenses for patients and contributes to improved adherence.
- **Evidence**: Liraglutide has been robustly evaluated in randomized trials dating back 10+ years, earning it the earliest approval for a GLP-1 agonist and making it the longest-studied agent in its class. Moreover, it is still actively studied in cutting edge trials today. Consider, for instance, the SCALE Kids trial, which appeared in the February 2025 issue of the New England Journal of Medicine and generated significant editorial discussion in the May 2025 issue. This drug is still highly relevant to the scientific and medical communities.
- **Clinical Benefits:** While the clinical efficacy liraglutide is sometimes discounted because it leads to fewer pounds of weight loss than semaglutide or tirzepatide, this view assumes that the benefits of GLP-1 agonists are mediated primarily by weight loss. However, weight loss explains only a fraction of the clinical benefits of this class of drugs. It is widely accepted, for instance, that the cardiovascular benefits of GLP-1 agonists are mediated by mechanisms independent of weight loss. This view is supported by several data points, including that the cardiovascular benefits emerge early after treatment initiation, often preceding substantial weight loss, and objective evidence that GLP-1 agonists improve markers of inflammation, a key contributor to cardiovascular events. The American Heart Association notes that the cardiovascular benefits of GLP-1 agonists are not solely attributable to improvements in glycemia or weight but also involve pleiotropic effects on vascular biology and inflammation.[4] Overlooking liraglutide

[4] Rangaswami J, Bhalla V, de Boer IH, Staruschenko A, Sharp JA, Singh RR, Lo KB, Tuttle K, Vaduganathan M, Ventura H, McCullough PA; American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on

because it leads to less weight loss than other GLP-1 agents ignores the fact that the benefits of these drugs go well beyond the pounds lost.

- **Side Effects**: Some argue that liraglutide has more side effects than semaglutide or tirzepatide, but the literature is somewhat mixed on this point. For example, the SUSTAIN 10 trial comparing semaglutide and liraglutide concluded both agents had similar overall safety profiles, with a higher incidence of GI adverse events (nausea, vomiting, diarrhea) with semaglutide versus liraglutide, leading to a higher discontinuation rate with semaglutide.[5] The STEP 8 trial, however, showed the opposite trend.[6] In both trials, the majority of these side effects were mild or moderate and occurred primarily during dose escalation. Meta-analyses have also pointed to a higher absolute rate of GI symptoms and total adverse events with semaglutide compared to liraglutide, while other data suggest that the tolerability profile is similar across the class.[7,8]
- **Utilization:** While current use of liraglutide is less than semaglutide or tirzepatide, many people still use it. Even a 5% market share in the massive and growing global market for anti-obesity drugs comprises millions of patients and hundreds of millions of expenditures. While publicly available peer-reviewed data is lacking, one platform (ClinCalc, which uses the Medical Expenditure Panel Survey from the Agency for Healthcare Research and Quality) reported that liraglutide was prescribed almost 2.2 million times in 2023.

Liraglutide is an FDA-approved agent for some of the most common medical conditions nationwide with proven efficacy and safety and is more affordable than its peers in a class of medications that is causing severe affordability challenges for health plans, employers, and patients. Understanding its relative cost-effectiveness is imperative not only for purchasers but also for society.

Self-insured employers, whose health care costs are rising much faster than inflation, are facing hard choices in their pharmacy benefits for employees.[9] Growing pharmaceutical spending has

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Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease: A Scientific Statement From the American Heart Association. Circulation. 2020 Oct 27;142(17):e265-e286.

[5] Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Vergès B, Marre M. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020 Apr;46(2):100-109.

[6] Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. JAMA. 2022;327(2):138–150.

[7] Xie Z, Yang S, Deng W, Li J, Chen J. Efficacy and Safety of Liraglutide and Semaglutide on Weight Loss in People with Obesity or Overweight: A Systematic Review. Clin Epidemiol. 2022 Dec 6;14:1463-1476.

[8] Kang YM, Punov V, Lim S, Nauck MA. Comparative efficacy and tolerability of currently approved incretin mimetics: A systematic analysis of placebo-controlled clinical trials. Diabetes Obes Metab. 2025 Jul;27(7):3736-3746.

[9] Abelson R. Health Care Costs for Workers Begin to Climb. The New York Times. September 4, 2025. https://www.nytimes.com/2025/09/04/health/health-care-costs-employers-workers.html

crowded out investment in the core business for some, while contributing to layoffs for others. Working families are also experiencing mounting financial pressure from growing drug costs, which are increasing premiums, deductibles, and in some cases leading to benefit losses. Similar trends are occurring in Medicare and Medicaid. If we are to successfully improve population health without bankrupting our nation's governments, businesses, and citizens, we must leverage the full cache of what science has to offer our patients. Liraglutide is part of that cache. The inconvenience of daily versus weekly injections is not inconsiderable but surely convenience is only one factor of many to consider when dealing with financial pressures at a scale that they contribute to job losses and affect economic growth.

Moreover, due to their need to be responsible financial stewards of limited resources, many public and private payers (including several large employers) do not cover *any* GLP-1 agonists for weight loss, which limits access for broad segments of the eligible population. A better understanding of the cost-effectiveness of liraglutide – and its presentation alongside its peers – may help demonstrate that this more affordable alternative to semaglutide or tirzepatide is an option they can responsibly cover, offering at least one GLP-1 agonist to patients who otherwise would have zero options (besides paying out-of-pocket through direct-to-consumer channels, a luxury that few can easily afford).

In conclusion, we believe that the inclusion of liraglutide in this analysis would enhance the social utility of ICER's report, better supporting the pursuit of value in anti-obesity medications and promoting affordability for employers and working families. Thank you for your attention to this comment and for your important work assessing the value of drugs.

Suhas Gondi, MD, MBA

Jonathan Mansour, PharmD, CSP

Tamara Howerton, BS, RPh

Logan Brinn, PharmD

Anja Kovacevic, PharmD

Joshua Bellamy, PharmD

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