Medications for Obesity Management
Response to Public Comments on Draft Evidence Report

August 31, 2022

Manufacturers

#	Comment	ICER Response
	Eli Lilly	
1.	In the Draft Report, ICER includes a scenario analysis of tirzepatide as "Drug X" which assumes the weight loss effects of tirzepatide based on the SURMOUNT-1 trial (incorrectly noted as "SUPPORT 1" on Page 42), pricing of semaglutide, and effects on blood pressure and diabetes mellitus similar to semaglutide. Ergo, ICER completed an assessment of tirzepatide in this Draft Report. While ICER offers that the rationale for including tirzepatide data from SURMOUNT-1 is to 'provide context' or to 'address... uncertainties' (page 41), we are not clear on how the inclusion of "Drug X" provides any additional context or addresses any uncertainties in your assessment of the four interventions in scope. Further, ICER did not include tirzepatide efficacy data in the clinical effectiveness portion of ICER's network meta-analysis, and it is unclear how these data were included in the comparative value analysis despite ICER's summary of the SURMOUNT-1 results in the Appendix. In addition, these assumptions used for "Drug X" are not reflective of the potential value of tirzepatide in obesity given that the price of tirzepatide for obesity is currently unknown and the SURMOUNT trials are still ongoing. Despite the lack of transparency in ICER's analysis, ICER goes on to provide an incremental cost-effectiveness ratio of "Drug X" followed by further results (page 48 and 49, Table 4.10). ICER also states, "Decision on the order of cost-effectiveness will be subject to the cost of tirzepatide achieving larger QALYs gained with a significant decrease in BMI compared to the currently available weight management strategies" (page 52). ICER did not include tirzepatide in any prior scoping documents for this assessment and, therefore, making these assumptions, providing results, and drawing conclusions related to tirzepatide within this assessment is inappropriate. Therefore, ICER should remove the scenario analysis of "Drug X," or tirzepatide, and all accompanying interpretations of this analysis as tirzepatide was not an intervention or comparator within the scope of this assessment. Lilly looks forward to engaging with ICER when additional data from our SURMOUNT clinical trial program is available, which includes four registration trials that thoroughly characterize tirzepatide for the treatment of obesity. Note that tirzepatide is also being investigated for additional benefits in obesity-related co-morbidities such as obstructive sleep apnea, heart failure with preserved ejection fraction and non-alcoholic steatohepatitis.	We agree with the concern that ICER and Eli Lilly did not have the opportunity for adequate engagement to allow for inclusion of tirzepatide in our evaluation of medications for obesity management. That is why we are not presenting an evaluation of tirzepatide. Rather, we are evaluating the effect of a drug with the specific weight loss results described in our analyses, some of which are based on weight loss results seen in the SURMOUNT trial. We are including this to give readers—who will be aware of SURMOUNT—a sense of how greater achieved weight loss, if applied to semaglutide, would affect cost effectiveness.

2.	Obesity is a complex multifactorial disease with numerous complications and comorbidities. On Page 41, ICER states, "Although we did not include some conditions that are known to be associated with weight loss, the anticipated benefit of weight loss in reducing the onset of such conditions was implicitly captured." ICER should explain how the model implicitly captures treatment benefits associated with other relevant comorbidities that are not captured by cardiovascular and diabetes complications, such as gastroesophageal reflux disease, back pain, gallbladder disease, liver disease, reproductive system disorders, gout, asthma, and cancer. Per the good research practices reported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Modeling Good Research Practices Task Force, ICER should choose a model structure that fully captures the complexity of obesity and all the conditions associated with treatment benefits. By choosing a simpler model approach, ICER's model structure excludes outcomes required to appropriately model the full health and quality of life effects resulting from the complex comorbid health conditions patients with obesity may face.	We agree that having Markov states for all obesity-related conditions—where supported by evidence of the effect of weight loss on the condition—would be preferable. However, due to the paucity of evidence regarding the causal association between obesity and non-cardiovascular conditions, and the impact of weight loss on these conditions, we chose to include only cardiovascular events where the causal association between the BMI change and clinical benefits was well established. Additionally, we were cautious about co-linearity (i.e., relationships between medical conditions included in the model resulting in the double-counting of benefits when included as independent variables in the model) across comorbidities, which results in over-estimation of the benefits of weight management. Finally, we assessed the potential impact of two conditions (CKD and cancer) that were omitted from the base case in a scenario analysis. Inclusion of these conditions in the model did not significantly affect the results. We believe that our current model explains the economic outcomes and quality of life influenced by the changes in BMI and is consistent with prior published models. Our approach should be able to reasonably capture the direct benefits of lifetime weight management on the health care sector cost and quality of life improvement.
3.	On Page 51, ICER noted an additional scenario analysis was conducted to "test the potential impact of weight loss on cancer risk and chronic kidney disease using add-on 'Comorbidity X' Markov states," but reported the incremental cost-effectiveness ratios were not significantly altered by the effects of these individual comorbidities. Further clarification of this conclusion is needed as the assumed impact of including both conditions would decrease the incremental cost-effectiveness ratios. Table E13 indicates each of these conditions reduces the cost-effectiveness ratio by about 10%. If ICER had included both these conditions in the base-case model, there may have been a reduction in the cost-effectiveness ratio by a significant percentage as modeling patients with multiple comorbidities has an additive effect on cost-effectiveness ratios. In addition, this scenario analysis only examines two comorbid conditions and does not examine all the possible relevant obesity-related complications that may impact weight loss. ICER should provide justification as to why these two conditions, along with other relevant comorbidities, were not included in the base-case model. ICER should also acknowledge the limitations of their model structure, which is unable to include multi-morbid states that could contribute to worse outcomes in patients and, therefore, underestimates the treatment benefits of anti-obesity medications in patients with multi-morbid conditions.	We appreciate your comments on the need of structured Markov chains to include more comorbidities associated with increased BMI. The purpose of including Comorbidity X was to test the effect of the inclusion of potentially important conditions in the model, rather than to assess the influence of specific conditions on the cost-effectiveness decision. Of the conditions either directly or indirectly associated with BMI change, CKD and cancer were selected to evaluate the impact of their inclusion on cost, mortality, and utility outcomes. Based on the results from the two Comorbidity X scenarios, we are confident that having non-cardiovascular comorbidity will have a nominal-to-moderate influence on the incremental cost-effectiveness ratio calculation. Importantly, CKD was not included in the base case because of the issue of collinearity between CKD and diabetes, which was included and already incorporated the costs and disutility of diabetes-related CKD. Cancer was not included in the base case due to the lack of evidence on long-term outcomes, including incident cancer, for each of the interventions in our scope, despite some recent evidence that bariatric surgery may be associated with lower rates of cancer.

4.	In Section E7, ICER also references prior economic models including a cost-effectiveness model of medication-assisted weight loss treatment strategies compared to lifestyle modification conducted by Kim et al. ICER notes "the incremental cost-effectiveness ratio estimates were generally lower than observed in our model and the structure, inputs, and assumptions of this model were considerably different from our model." Comorbidities included in the referenced model were post-myocardial infarction (MI), type 2 diabetes, post-stroke, obstructive sleep apnea, and cancer. Also, in the 2022 NICE appraisal of semaglutide for managing overweight and obesity, comorbidities such as non-diabetic hyperglycemia, type 2 diabetes, obstructive sleep apnea, acute coronary syndrome, stroke, and osteoarthritis were included to determine the cost-effectiveness of semaglutide. By excluding such conditions, ICER's model may not be fully capturing treatment benefits for obesity. We advise that ICER report the differences in assumptions in these models and address the limitations of omitting relevant obesity-related comorbidities in the model structure. Further, ICER should acknowledge that they are not fully capturing the potential value of anti-obesity medications in the cost-effectiveness results of this assessment.	We did not include the conditions listed for several reasons: 1) the conditions in the 2022 NICE appraisal would have a nominal influence on the cost and QALYs estimate; 2) benefits of having such conditions would be captured by the estimated decrease in the cardiovascular mortality; 3) there is insufficient evidence on the causal association between weight loss and decrease in the onset of condition; and 4) we were concerned about multicollinearity in the model, leading to overestimation of the weight-loss benefits.
5.	ICER should provide more clarity on the primary risk equation used in the model of this report and conduct sensitivity analyses that demonstrate the impact alternative risk equations may have on the model outcomes. On Page 40, ICER states, "The annual risk of developing cardiovascular conditions at the beginning of each cycle was calculated using a published risk equation model based on BMI, presence of diabetes mellitus, population demographics, and clinical characteristics. Specifically, the 2013 ACC/AHA guideline risk equation was used to calculate the 10-year risk of non-heart-failure cardiovascular conditions." This 2013 guideline on cardiovascular risk reviews risk factors and includes an update of the Framingham risk equation by D'Agostino et al (Pooled Cohort Risk Equations, Appendix 7, Table A) which does not include BMI as a risk factor. However, the 2008 Framingham risk equation by D'Agostino et al includes office-based measures that appear to align with what ICER claims to have used in their risk equation model and includes BMI as a risk factor. ICER should therefore provide more specific details around the risk equation source, parameters, and variables used in their model to allow stakeholders to clearly follow how risk is being calculated.	We have included the equations and coefficients in both the Report and Supplement. We agree regarding the benefits of using recently advanced risk calculation methods, such as UKPDS or QRISK. However, even with potential limitations, ICER decided to use the non-laboratory risk equation from the Framingham cohort because: 1) long-term changes in metabolic outcomes resulting from BMI change are not available for all therapies evaluated; 2) differences between study populations enrolled in the cohort used to develop the QRISK risk equation or UKPDS model and our study cohort; 3) previous cost-effectiveness studies had already tested the feasibility of using non-laboratory-data based Framingham risk equation and validated their results with observational outcome data; and 4) the Framingham Risk Equations and 2013 ACC/AHA guideline risk equations have been well validated, with a thorough evaluation of their performance available in the literature.

	ICER should explain the approach used to select the primary risk equation in the model and conduct scenario analyses using different risk equations. There are several potential risk equations that could be used, each with its own advantages and limitations. For example, the QRISK2 risk equation includes BMI and has been shown to better predict cardiovascular risk compared to the 2008 Framingham risk equation, but is based on UK data and may not reflect a US patient population with obesity. The 2008 Framingham risk equation is widely used and was used in the 2022 NICE appraisal of semaglutide as a scenario analysis (NICE used the QRISK3 as the base-case primary risk equation), but may reflect an outdated population that may not be representative of the patient population with obesity today, does not account for changes in treatment patterns, treatment landscape, and prevalence of risk factors related to obesity, and utilizes limited office-based measures. The decision of which risk equation to use has the potential to significantly alter the results of the model, including the estimate of cardiovascular risk. ICER should therefore provide an explanation for their selected primary risk equation, share details on its limitations, and conduct scenario analyses to show the impact different risk equations have on the model outcomes.	
6.	ICER should evaluate several plausible time horizons including two, five, ten, and lifetime treatment durations to reflect varied clinical assumptions and uncertainties around utilization and benefit of anti-obesity medications over time. On Page 50 of the draft evidence report, ICER cites research from the GAO reporting medication durations of 91 days or less in nearly 80% of patients with first treatment episode, but expert input indicated lifetime treatment duration is the "preferred approach" in obesity. While clinically advisable, ICER's use of a lifetime duration for the base-case analysis does not reflect real-world utilization. In comparison, NICE assumes a maximum treatment duration of two years in the base-case of their 2022 appraisal for semaglutide. NICE notes they recognize that obesity is a lifelong condition but there is a lack of evidence on long-term use and benefits. Results of cardiovascular outcomes trials for oral semaglutide 14 mg, 0.5 mg/1.0 mg semaglutide, and 1.8 mg liraglutide in type 2 diabetes indicate significant mean differences in cardiovascular benefits between the GLP1s and placebo were seen around five years. Therefore, a proxy of five years could be used to simulate the impact of anti-obesity medications on long-term use and benefits in weight management.	We appreciate your support of using lifetime perspective as part of our base-case model in the draft Evidence Report. We understand the benefits of life-long medication may raise questions. However, weight regain after the short-term use of anti-obesity medication is evident. Further, it is possible that such weight regain and related weight cycling may have adverse cardiovascular and other health effects. With respect to this potentially clinically undesirable weight regain trajectory, our clinical advisory group has been supportive of recommending modeling life-long weight management with medication unless patients cannot tolerate the regimen. Previous model-based cost-effectiveness assessment employed published risk equations, such as the UKPDS model or cardiovascular risk equations from Framingham cohorts, and annualized the long-term risk to calculate per-cycle risk. The validity of the annualizing of long-term risk estimates for assessing the impact of temporary weight change on cardiovascular outcomes has not been rigorously tested. In testing our model evaluating short-term treatment on lifetime cost effectiveness, we discovered a counterintuitive finding. Specifically, risk equations to estimate cardiovascular risk predicted complete avoidance of cardiovascular events during treatment, rather than a delay in the cardiovascular event. This result is not consistent with our understanding of the pathology of cardiovascular disease and leads to a

		likely overestimation of the benefits of short-term treatment. Therefore, due to the uncertainty in the true benefits of temporary weight loss following short term use of anti-obesity medications, we chose to omit shorter treatment times until additional evidence can be generated evaluating the impact of stopping weight-loss therapy (and the subsequent weight gain) on cardiovascular outcomes.
7.	On Page 15 of ICER's model analysis plan, ICER stated they will include a weight regain scenario, in which "patients will be assumed to discontinue weight management intervention after the second year, which will be followed by weight regain over time" and will simulate the "lifetime benefits and cost-effectiveness of the short-term weight management." However, the results of this scenario analysis are not included in the draft evidence report, and ICER should provide explanation for their omission. It is critical that ICER addresses the uncertainties around weight regain trajectory and optimal treatment durations, such as the lack of data surrounding the long-term use and outcomes of anti-obesity medications, and exercise due diligence by conducting additional scenario analyses that align with the good research practices reported by the ISPOR Modeling Good Research Practices Task Force. Therefore, Lilly recommends assessing several plausible time horizons to simulate treatment durations of two years, five years, ten years, and lifetime to reflect varied clinical assumptions and uncertainties around utilization and benefit of anti-obesity medications.	First, we would like to clarify that treatment duration and time horizon are two different concepts. ICER employs a lifetime time horizon for all analyses, as is the current best practice recommendation. With regards to treatment duration, we removed shorter treatment durations from our assessment based on inconsistent findings with this scenario. As described above, using risk equations to estimate cardiovascular risk predicted complete avoidance of cardiovascular events during treatment, rather than a delay in the cardiovascular event. The Report will be updated to remove this scenario from the methods section until more evidence can be generated to evaluate the impact of stopping short-term weight loss treatment on cardiovascular risk in the period immediately following discontinuation.
8.	In general, for this report and any revised draft evidence reports, ICER should clearly state the corrections and changes made in order to provide full transparency to stakeholders.	Thank you for your comment. We review all comments and try to make clear what changes are made in response to them.
9.	Explanation of which input values and sources were utilized to model the caregiver and productivity costs used to calculate the indirect costs included in the scenario analysis from a societal perspective.	Thank you for your comment. We have included the source of the indirect cost calculation in Supplement Table E11.
10.	Inclusion of full disaggregated results with non-drug costs and cumulative incidence of the different types of cardiovascular events, including heart failure, and diabetes for all model arms across the full model time horizon would help assess what is occurring in the model. This would align with modeling best practices. For example, on Page 50, ICER states the model estimated the cumulative incidence of cardiovascular conditions at 59.5% in patients receiving lifestyle management. Lilly recommends ICER provide cumulative incidence rates of cardiovascular disease over time for all treatment arms in a figure to allow users to assess and validate the model.	We appreciate your interest in further details of the clinical outcomes projected. We included the cumulative incidence of cardiovascular events and overall survival in the Supplement.
11.	Clarification on why the draft report and appendix do not present the scenarios and corresponding results that model a patient cohort with an average BMI of 50 kg/m2,	Our population of interest and scenario analyses were determined based on expert opinion during scoping as well as the availability of data for all treatments. Some

	a real-world population (50% females, 50% males), pre-diabetes cohort, discontinuation, weight regain, and inputs comparable to a recent cost-effectiveness analysis with lifetime and two-year treatment duration. Stating that an analysis was completed, without providing the results, is not sufficient to help the reader understand the impact or results of the analysis.	scenario analyses we proposed in the Model Analysis Plan could not be performed due to the lack of reasonable inputs and assumptions. The results for a subpopulation of patients with a BMI equal to or greater than 40 (i.e., weight class III with average BMI of 42.5 and 47.5 kg/m^2) were omitted from the draft Evidence Report. These have been added to the Supplement for the revised Evidence Report. Real-world populations of patients treated with anti-obesity medications typically include a higher proportion of female patients. As such, the base case does represent a real-world population. A scenario analysis evaluating a patient population consisting of a similar proportion of men and women was omitted from the draft Evidence Report. This has been added to the Supplement for the revised Evidence Report. Scenarios evaluating the short-term treatment, including discontinuation and weight regain, were evaluated, and removed from the Report due to a potential overestimation of benefits that is likely to occur when using risk equations to predict lifetime cost effectiveness with short-term treatment, as described in a previous response. The benefits of semaglutide and liraglutide in patients with diabetes has already been evaluated. Our model was designed to evaluate the impact of semaglutide in patients without diabetes (or pre-diabetes) and, with the exception of delays to onset of diabetes, did not include the impact of treatments on HbA1c. Therefore, we omitted from the Report the analysis evaluating patients with diabetes.
12.	ICER assumed that MI was a prerequisite to developing heart failure because of the strong causal association between obesity and heart failure mediated by myocardial changes. However, this assumption may underestimate the incidence of heart failure and implicated costs. ICER should further explain the underlying evidence for this assumption as it implies that rates of heart failure are lower than MI, when there are several studies that suggest rates of heart failure are higher than rates of MI in patients with obesity or that MI is only one of several different pathways in which obesity leads to heart failure.	We acknowledge that this is a limitation of our analysis. We assumed that hypertension and diabetes management would be optimal across all populations, regardless of weight management treatment. Therefore, the incremental impact of medications for weight loss on non-ischemic heart failure incidence would be expected to be minimal. In addition, there was concern about multicollinearity in the different pathways to heart failure and a considerable possibility of overestimating the benefits of medications for weight loss on heart failure.
13.	ICER captures the increased risk of secondary cardiovascular events through the annual probabilities of recurrent MI and stroke in Table E4, but it is unclear if ICER used secondary risk equations or applied an additional risk of MI and stroke to patients who have already had an event. ICER should provide additional clarification on how the increased risk of secondary events is included in the model.	We included the rate of recurrent event and cited references in Supplement Table E4.

14.	In the ICER model analysis plan, ICER indicated they will validate the incidence of heart failure, but these figures are not reported in the draft evidence report.	We appreciate your question on the further details of the study findings. Changes were made to the model between the Model Analysis Plan and the draft Evidence Report. The cumulative incidence of heart failure was not included in the draft Evidence Report because the model only captured and reported heart failure due to myocardial infarction. As described above, this would reasonably capture weight-related changes in the rate of heart failure, but would not precisely estimate the overall heart failure incidence. Since there are not good literature estimates for the incidence or prevalence of heart failure occurring due to myocardial infarction only in this patient population, heart failure estimates were not presented or validated.
15.	In Table 4.2, ICER provides the comorbidity annual cost inputs for post-stroke and post-MI states. ICER should provide more detail on how the post-MI state was utilized in the model as no post-stroke or post-MI states are described or shown in the model diagram (Figure 4.1). ICER also reports annual cost of heart failure as $15,605, but a systematic review estimated median annual heart failure costs as $24,383 in the US.	We revised the model diagram and input tables to add clarity.
16.	ICER should include clear details in the report on the following areas: • How is treatment effect durability applied throughout the model? • How is progression from pre-diabetes to diabetes accounted for in the model? On Page 44, in Table 4.2, the inputs used to estimate the effect of HbA1c and BMI on the annual incidence of diabetes mellitus are based on an exponential regression of data from Edelman et al. ICER should provide additional details and clearly explain how these inputs were derived from the reference and utilized in the model to estimate the incidence of diabetes. • Why is the 15 mg/92 mg dose of Qsymia utilized in the model despite the 7.5 mg/46 mg dose being recommended in the prescribing information for Qsymia? (Dose escalation to the 15 mg/92 mg dose is recommended if ≥3% weight loss is not achieved.)	We appreciate your comment on the need for further descriptions. In the revised Evidence Report, we describe the tolerance to the anti-obesity medication and how we included such information in the cost calculation. The input table includes the diabetes risk based on HbA1c and BMI. We chose to model the maximum dose and effect of Qsymia with the understanding that clinicians would attempt to maximize weight loss, provided that patients tolerated treatment.
17.	ICER should clearly distinguish the scenarios that will be examined in the clinical section versus those that will be examined in the modeling section if they expect those to differ. • On Page E3, ICER states the target population had HbA1c of 5.5% at model entry; this is at odds with the 5.7% figure on Page 39. • On Page E11, Table E8, ICER should clarify if the incremental cost-effectiveness ratios presented are for the undiscounted results as the section heading suggests. The results appear to be identical to the discounted results presented in Table 4.6.	There exists a nominal difference in the patient characteristics between the clinical and economic sections, depending on whether data is being presented from the entire population, as in the clinical section, or a specific subgroup such as in the model. Thank you for pointing out this editing issue. The table results have been updated with new results, correctly displaying undiscounted numbers.

Novo Nordisk		
1.	We would stress that the ICER team consider incorporating the risks of obesity and the benefits of weight loss on all-cause mortality into the base-case cost-effectiveness analysis. The Global BMI Mortality Collaboration published a meta-analysis of data from 239 prospective studies with over 10 million participants and found that among patients who survived for at least 5 years, all-cause mortality risk increased steadily for patients who are overweight and obese (see Table 1 in the appendix). Three other studies support this general trend of higher risk of all-cause mortality as BMI increases above normal for a variety of different population subgroups. Furthermore, increasing risks of cause-specific mortality as BMI increases above the normal range were also demonstrated in a database study of the UK Clinical Practice Research Datalink2.	In developing our cost-effectiveness model, we sought information demonstrating decrease in all-cause mortality for the medications included in our analyses. Semaglutide, as well as the others included in our Report, have not demonstrated reductions in all-cause mortality. Despite the lack of such information, our model does include changes in mortality that may occur as part of preventing serious cardiovascular events. Thus, in spite of the lack of such evidence, our model does permit changes in mortality brought about through the prevention of cardiovascular disease. Additionally, including further mortality reductions resulting from weight loss alone would have double-counted possible mortality benefits of medications for weight loss.
2.	As described in the DER, the base-case cost-effectiveness analysis includes only type 2 diabetes and CV comorbidities in the model. The justifications provided in the DER include uncertainty in the causation of weight on additional comorbidities and the assumption that the comorbidities will have little impact on outcomes. The DER includes scenario analyses that consider the addition of cancer and chronic kidney disease in separate scenarios, and the analyses do not account for the impact of these comorbidities on health-related quality of life. As the CDC notes that 40% of cancers diagnosed in the US are associated with overweight and obesity, these scenario analyses are critical and based on our experience supporting research in obesity, a model without due consideration to the several obesity-related comorbidities may not capture the clinical presentation of such a complex disease as obesity comprehensively.	We appreciate your attention to specific details of the comorbidity trajectory. We have acknowledged the potential limitations of excluding several conditions in the model. As described in our response to a similar question above, we were primarily concerned about double-counting the benefits of weight loss on CKD outcomes, as CKD was included in the cost and disutility estimates for diabetes. Cancer was not included in the base-case analysis because of low incidence and likely low impact on the incremental cost-effectiveness estimates. We conducted a scenario analysis that included each of these conditions separately. We also note that while ICER conducts its reviews independently, a recent CADTH recommendation against Wegovy coverage was predicated on the trialists' failure to demonstrate that Wegovy improved weight-related comorbidities. We believe we have given Wegovy the benefit of the doubt by accounting for appreciable weight-related comorbidity benefits, but we do not find it warranted to assign additional weight-related comorbidity benefits that may represent double-counting of treatment effect or is inadequately evidenced regarding long-term treatment with Wegovy.
3.	Based on available evidence as well as NN's experience in developing economic models for anti-obesity medications (AOMs), we encourage ICER to include the costs and utilities of a comprehensive list of comorbidities associated with obesity in the base-case cost-effectiveness analysis, including OSA, CKD, osteoarthritis, asthma, and NAFLD & NASH.	As described in a response to a similar comment above, our Report did not include some of the conditions listed for several reasons: 1) the conditions listed in recent appraisal or previous study would have a nominal influence on the cost and QALYs; 2) benefits of such conditions would be captured by the estimated decrease in the cardiovascular mortality and BMI-related health utility; 3) there is insufficient evidence on the causal association between the medically-managed weight loss and decrease in the onset of the conditions; and 4) we were unable to properly adjust for the double-counting and multicollinearity problems using the current model-

		based cost-effectiveness assessment frame, leading to overestimation of the weight-loss benefits.
4.	To avoid double counting, ICER could perhaps consider only including costs for CKD that are not part of the costs for diabetes and other comorbidities by using a source that disaggregates the costs of CKD, such as the cost-effectiveness analysis published by Kalantar-Zadeh (see Figure 5 in the appendix). The Kalantar-Zadeh publication also has health-state utilities by CKD stage that may be incorporated into the analysis.	We appreciate your comment. The explicit costs of CKD were modeled in a scenario analysis and showed a relatively small effect on the incremental cost-effectiveness ratio.
5.	Our opinion, based on literature and clinical expertise, is that the model should account for a portion of HF not associated with MI and should include the impact of obesity on HFpEF. If this is not possible, we recommend that this be noted as a limitation.	We acknowledge that this is a limitation of our analysis. We assumed that hypertension and diabetes management would be optimal across all populations, regardless of weight management treatment. Therefore, the incremental impact of medications for weight loss on non-ischemic heart failure incidence would be expected to be minimal. In addition, there was concern about multicollinearity in the different pathways to heart failure and a considerable possibility of overestimating the benefits of medications for weight loss on heart failure.
6.	The model analysis plan stated that the cost effectiveness of AOMs in patients with BMI ≥40 kg/m2 (Obesity Class III) would be evaluated in a scenario analysis. No such scenario analysis is presented in the DER. In addition, the Obesity Class III subgroup alone represents a small proportion (~15%) of the obesity population (Figure 7). To ensure that the model developed by ICER not miss capturing the impact of interventions for persons living with obesity and overweight who may benefit from therapeutic interventions, we strongly recommend that ICER include subgroup analyses for each obesity class and not limited only to patients with BMI ≥40 kg/m2 (Obesity Class III). A study by Evans and colleagues not only reported that healthcare costs differ across obesity classes, but that patients incurred greater healthcare costs even after spending 8 years in the same obesity class. NN has provided pertinent information to ICER about semaglutide and liraglutide by obesity classes during the data request phase. We believe that thorough subgroup analyses of all obesity classes will provide useful information for payers in determining coverage policies for AOMs.	The results for a subpopulation of patients with BMI equal to or greater than 40 (i.e., weight class III with average BMI of 42.5 and 47.5 kg/m^2) were omitted from the draft Evidence Report. These have been added to the Supplement to the revised Evidence Report. Given the minimal difference in the incremental cost-effectiveness estimates when comparing the base-case population and those in weight class III, we do not believe that additional analyses by weight class are necessary.
7.	The DER states that "percent weight change … from baseline at year one and maximum percent weight change by the end of the second year were incorporated into the [cost-effectiveness] model" (p. 43). However, it does not report how those estimates are sourced, nor does it clarify the approach used for Contrave®, for which 2-year data are not available.	We added a description about how the maximum efficacy in weight management was utilized in the model. Please see Supplement page E7.

	Kindly clarify the sources and estimates for maximum percent weight change by the end of the second year. We recommend using actual weight loss observed in high-quality studies that have been carried out for this duration, where those data are available: Wegovy® (STEP 541), Saxenda® (SCALE Obesity and Prediabetes42), and Qsymia® (SEQUEL43). Gaps in the available evidence (e.g., Contrave®) should also be noted as a limitation of the analysis.	

Research and Patient Organizations

#	Comment	ICER Response
	Southern Christian Leadership Conference	
1.	ICER's model does not include (or count) the significant harms of obesity in patients under age 45, including failing to count complications for women of childbearing age. ICER focused its model on patients over 45 years of age. Accordingly, the long-term benefits of obesity treatments in younger adults, including women of childbearing age, were not counted in the review. We associate ourselves with the detailed comments (including citations) in the Diversity Stakeholders letter on this issue. The recent Supreme Court reversal of Roe v. Wade has led many states to adopt highly restrictive state abortion laws, especially those with some of the highest obesity prevalence and maternal morbidity/mortality rates. Obesity will certainly complicate health outcomes for women in these states who will be forced to carry unplanned pregnancies to term.	The model uses the average age of patients who participated in the trials of medications for obesity. We agree that preventing and treating obesity should include younger individuals. None of the studies we reviewed considered the potential effect of weight reduction on fertility. It is possible that fertility, maternal morbidity and mortality, and infant health may be improved with weight loss. We recognize that this is a limitation and may be a potential other benefit of effective obesity treatments. Of note, all of the treatments studied in this report are not recommended for pregnant women. Women who are taking one of these medications at the time a pregnancy is diagnosed would be advised to stop taking the medication.
2.	SCLC urges ICER to retool its analysis to account properly for all likely benefits of anti-obesity medications, including healthcare costs avoided by successful treatment, in its final Evidence Report. We acknowledge that the relationship between obesity and other chronic conditions is complex, and it is difficult to assign monetary costs to all potential obesity related complications and comorbidities; but ICER should incorporate an estimated range when supported by science and logic. Also, there are meaningful differences in subpopulation prevalence, outcomes, and response to alternative treatments. As such, a value assessment aggregating data into a single value calculation will tend to under-value interventions that have higher value in those subpopulations. For the purposes of the obesity review, People of color and other underserved populations are under-studied and under-represented in clinical trials. Accordingly, ICER would improve the accuracy of its reviews if it either performed subpopulation scenarios or extrapolated disparate data to simulate the impacted population, disease burden, and treatment response. SCLC associates itself with the examples of key inputs to which the Diversity Stakeholders letter refers.	One aim of the economic assessment is to assess the health care costs avoided by successful treatment. The likely benefits of anti-obesity medications, as supported by evidence, have been included in the model. Our Report included cost offsets and savings in the non-intervention cost. We acknowledge that the results of the model are limited by data available from clinical trials and/or real-world evidence. Where reliable evidence was available to adjust results to a more real-world scenario, we incorporated such data in the model. Note that ICER does not have access to data from clinical trials and cannot conduct subgroup analyses. We are reliant on published data or analyses provided by manufacturers of the reviewed medications.
3.	Moreover, the model does not consider ongoing weight gain in patients failing behavioral interventions and not receiving anti-obesity medication or reduced effectiveness of behavioral interventions in individuals of color. Economic models typically assign utility increments/decrements for incremental	Thank you for sharing your concerns about weight gain over time in patients with lifestyle modification with or without medications for weight loss. These results were included in one-way sensitivity analyses and not in separate scenarios. Weight gain had a relatively minor impact on the incremental cost-effectiveness estimates.

#	Comment	ICER Response
	decreases/increases in BMI. So, a range of decrements should be assigned to the base case calculations for behavioral interventions alone.	
4.	Finally, the Draft Evidence Report did not include 2021 evidence demonstrating that Semaglutide's effectiveness is similar across races and that it is actually more effective in individuals on the lower-BMI levels of obesity and in female patients.	In response to this comment, we have added details to the Report describing published data regarding differences in weight loss by specific subgroups including race and ethnicity.
Black Women's Health Imperative		
1.	We urge ICER to approach its valuation of anti-obesity medications within the context of the scope of the obesity epidemic and the current under-utilization of this aspect of evidence-based obesity care. We remain concerned that an analysis that fails to fully consider the long-term impact that obesity has on the health and lives of our communities, and the added value of pharmacotherapy in managing obesity for many patients, will further entrench health system reliance on behavioral interventions alone.	As highlighted in the background section of our Report, we detail the broad scope of the obesity epidemic, the misperceptions about the underlying causes of obesity, and the need to improve available treatments for those with obesity. Though we received feedback that the lifetime horizon in our cost-effectiveness model does not reflect the real-world use of medications, we have focused on a lifetime horizon for the reasons cited – to assess the long-term impact that obesity has on the health of individuals with obesity. Indeed, two of the medications we evaluated demonstrated very favorable cost-effectiveness ratios. This clearly supports the potential role of these medications to improve the health of these patients.
2.	ICER should incorporate the disproportionate burden of type 2 diabetes (T2D) on communities of color into its analysis of obesity interventions. As ICER has previously noted, communities of color are disproportionately impacted by T2D – from prevalence of risk factors (e.g., obesity) to new T2D diagnoses, complications, progression to ESRD and/or limb amputations, and even death. Obesity is a primary driver of T2D and compromised health outcomes for Black women in prevalence and health outcomes. In fact, the greatest disparity in subpopulation T2D rates are between Black women and white women; and appear to be due to risk factors such as obesity. (NIH, Schneider, 2002) In addition, we urge ICER to ensure that its inputs reflect the lived experience of Black women and girls with respect to disparities and inequities in health outcomes throughout the T2D disease trajectory – from risk factors and disease prevalence through increased disease severity, complications, morbidity, and mortality. • Black adults are 60 percent more likely than non-Hispanic white adults to be diagnosed with diabetes by a physician, twice as likely to die from T2D, and 3.2 times more likely to progress to ESRD when compared to their white counterparts. • Black Medicare beneficiaries with diabetes are more likely to receive lower quality care and have diabetes-	We agree that a key potential benefit of treatments for obesity would be to prevent diabetes and the complications that can be associated with it. As such, our model focuses on individuals who do not have diabetes and follows them over the course of their lifetime. The goal is to demonstrate the potential effects of weight reduction on comorbid diseases over time. As noted, diabetes does greatly impact communities of color and therefore our findings are directly relevant for this group. More data is needed on the relative effects of medications to treat obesity among different groups. As noted previously, the effects of semaglutide on weight loss is similar across individuals who self-report different racial groups. This suggests our findings may apply across racial groups. However, there is less data across racial groups on weight loss outcomes among the other medications we evaluated. In terms of the potential for weight loss to decrease kidney disease, we did not include this in our cost-effectiveness model for reasons previously noted.

#	Comment	ICER Response
	related complications, such as end-stage renal disease, chronic kidney disease, and amputations (Goodney 2013). • Black patients are significantly overrepresented in the ESRD population, making up nearly one-third of the half-million US ESRD patients. • Black women on dialysis are less likely to receive an adequate dialysis dose, have a fistula placed, and achieve target hemoglobin levels. These metrics are associated with decreased dialysis survival (Kucirka 2011). • Although kidney transplant is the standard of care for ESRD patients, Black patients are far less likely to have kidney transplant as an available option. Racial disparity in kidney transplant waitlisting persists even after adjusting for medical factors and social determinants of health. • Black transplant recipients experience poorer outcomes, including higher rates of kidney rejection and patient death, than white transplant recipients.	
3.	We urge ICER to ensure that its model reflects divergence among subgroups (sex, race, ethnicity) in obesity complications, including cardiovascular disease, and health outcomes. (Levy 2002; Gerber 2015) • Hypertension and diabetes play a greater role in the development of coronary artery disease in women than in men; thus, they also directly or indirectly play a significant role in the development of heart failure in women. • Incidence rates of heart failure in Black women were more similar to those of men than of white women. • Compared to men, women with heart failure have higher frequency rates of dyspnea on exertion, difficulty exercising, and edema. (Levy 2002; Gerber 2015) • Despite controlling for age, ejection fraction, and New York Heart Association classification, women tend to have worse quality of life ratings than men for intermediate activities of daily living and social activity. • Depression is more common in women with heart failure than in men.	We agree on the value of subpopulation-specific estimates when the anticipated benefits would not be the same across subgroups. To address the questions on the subgroup-specific estimates, however, more data is needed on the relative effects of medications to treat obesity among different groups. We acknowledge the limitations of using the 2013 ACC/AHA guideline risk equations for predicting cardiovascular outcomes. Where possible, we tested the influence of varying several key clinical, economic, and quality of life/utility characteristics in sensitivity analyses.
4.	ICER's recent evidence report in T2D included calculation of the Health Improvement Distribution Index for T2D. This index is intended to acknowledge and quantify increased subpopulation health gains in disease states that disproportionately impact identifiable subpopulations. BWHI appreciates that ICER seeks to incorporate a societal goal of reducing health disparities and inequities within its value framework. Use of the Health Improvement Distribution Index is a helpful tool toward that goal, but it	Thank you for your comments related to highlighting disease burden across potentially socioeconomically disparate groups. In its current form, the Health Improvement Distribution Index evaluates the relative potential health gains across identified subpopulations within the overall population of affected individuals in the US. As such, the Health Improvement Distribution Index helps characterize opportunities for relatively greater health gains within subpopulations that have been subject

#	Comment	ICER Response
	does not fully capture the potential benefits of anti-obesity medications in Black women and other people of color. Ideally, ICER's framework would: • Incorporate disparate prevalence among subpopulations as one factor in calculating potential health improvement. In obesity, disparities in health outcomes extend beyond cardiovascular consequences to include new T2D diagnoses, progression to ESRD, poorer prognosis. within ESRD, increased rates of limb amputations, vision loss, and higher mortality rates, increased breast cancer mortality, obesity impact on fertility and adverse pregnancy outcomes. • Account for disparate health benefits within the base case and/or subpopulation scenarios to capture the potential that increased health gains can increase value from both the health system (payer) perspective and the societal perspective. • Incorporate a treatment's potential to reduce health disparities within contextual considerations as an "added" benefit of a new treatment while also quantifying the potential health and productivity gains among subpopulations within the base case and societal perspective scenarios.	to disparities in access to care and/or health outcomes. Presently, the Health Improvement Distribution Index is calculated as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. A Health Improvement Distribution Index above one suggests that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a Health Improvement Distribution Index of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. Policymakers may wish to give greater priority to interventions that have a potential benefit of helping reduce health disparities. To keep the Health Improvement Distribution Index messaging concise, we suggest considering at most two Health Improvement Distribution Index subgroups per assessment. Further, we only consider prevalence at this time to keep the Health Improvement Distribution Index approach clear and concise as well. This may be subject to change in the future.
5.	BWHI continues to urge ICER to include outcomes, costs, and utility values that are important to women of childbearing potential. The increasing prevalence of overweight and obesity in younger populations combined with the challenges of excess maternal morbidity and mortality Black women face heightens the importance of ensuring access to all medical care with potential to improve outcomes. This includes, when possible, ensuring that patients have an opportunity to address obesity before becoming pregnant and are provided the full set of interventions needed to address pregnancy weight gain as appropriate.	As previously noted, we agree that preventing and treating obesity in younger individuals, particularly women of childbearing age, is important. None of the studies we reviewed considered the potential effect of weight reduction on fertility. It is possible that fertility, maternal morbidity and mortality, and infant health may be improved with weight loss. We recognize that this is a limitation of our analyses. We have added this in our discussion of potential other benefit of effective obesity treatments.
6.	BWHI urges ICER to incorporate a "range" of health outcome impacts and costs beyond those associated with cardiovascular disease in its model and analysis. This should include obesity-related diseases and complications such as breast cancer (Picon-Ruiz 2017), non-alcoholic fatty liver disease (Sarwar 2018), and other obesity-related conditions (Milken 2020). We also urge ICER to fully incorporate the costs of lost productivity into its societal perspective, and to present that scenario as a co-base case. (Milken 2020)	We appreciate your suggestions to expand the scope of obesity-related conditions and outcomes. Because of the debate on the scope of obesity-driven complications and productivity loss following the onset of the conditions, ICER placed the societal perspective assessment in the scenario analysis section, even though many previous studies performed by ICER considered the societal perspective as co-base case.

Combined Stakeholder Public Comments		
1.	ICER focused its model on patients over 45 years of age. This means that the long-term benefits of obesity treatments in younger adults, including women of childbearing age were not considered. • Gestational diabetes is linked to obesity • US Hispanics/Latinas are at two- to fourfold higher risk for gestational diabetes compared with non-Latina whites (Ferrara 2007; Fujimoto et al. 2013) • Black women are generally less likely to suffer from gestational diabetes, but those who do are more likely to be obese and far more likely to subsequently develop Type 2 diabetes • Cardiologists and gynecologists recommend that women address obesity before becoming pregnant. In 2019, over half of the young women (20-44 years of age) giving birth had at least one cardiovascular risk factor • Overweight and obese women are more likely to suffer from infertility. This can have a life-changing impact on women of color who do not enjoy the same level of access to fertility treatments as their white counterparts (Lake 1997) • Pre-pregnancy obesity is associated with increased risk of poor fetal and maternal outcomes including miscarriage, pre-eclampsia, surgical complications, and heart and neural tube defects • Obesity may interfere with the pharmacokinetics of emergency contraception ("Plan B"), reducing its effectiveness in women with a BMI over 30 (Edelman, 2016) …The impact of obesity on women of childbearing age is of greater urgency now than it was when ICER started its review; it should be included in the model within the base case and societal perspective as well as in the set of contextual considerations.	Thank you for your comment. Please see our prior responses. We agree on the value of subpopulation-specific estimates when the anticipated benefits would not be the same across the subgroups. To address the questions on the benefits of weight-management in subgroups, more quantitative data is needed on the relative effects of medications to treat obesity among different groups. We note the scope of our research is currently limited to patients who can and are willing to take the life-long intervention. ICER is willing to expand the scope of our assessment to women of childbearing age if specific trajectories and outcomes are available.
2.	ICER should ensure that all avoided costs and likely benefits of anti-obesity medications are factored into the final Evidence Report. We recognize that the relationship between obesity and other chronic conditions is complex and that assigning monetary costs to the full range of potential obesity outcomes, complications and comorbidities with precision and certainty would be nearly impossible. We continue to believe that ICER should incorporate an estimated range when science and its logical interpolations/extrapolations make the uncertainty of a particular outcome or finding a matter of increments or degrees.	Thank you for your comments. We agree that addressing all obesity-related conditions, where supported by evidence of the effect of weight loss on the condition, would be preferable. However, due to the paucity of evidence regarding the causal association between obesity and non-cardiovascular conditions, and the impact of weight loss on these conditions, we chose to include only cardiovascular events where the causal association between BMI change and clinical benefits was well established. Additionally, we had to be cautious about collinearity (i.e., relationships between medical conditions included in the model resulting in the double-counting of benefits when included as independent variables in the model) across comorbidities, which results in over-estimation of the benefits of weight management. Finally, we assessed the potential impact of

		two conditions (CKD and cancer) that were omitted from the base case in a scenario analysis. Inclusion of these conditions in the model did not significantly impact the results. We believe that our current model explains the economic outcomes and clinical events influenced by the changes in BMI and is consistent with prior published models. Our approach can reasonably capture the direct benefits of life-time weight management on the health care sector cost and quality of life improvement.
3.	Similarly, there are meaningful differences in subpopulation prevalence, outcomes, and/or response to alternative treatments; a value assessment aggregating data into a single value calculation will tend to under-value interventions that have higher value in those subpopulations. Black and Latinx patients and other underserved populations are under-studied and under-represented in clinical trials and, unfortunately, most likely to suffer compromised health outcomes from treatment delays and/or denials. ICER would improve the accuracy of its reviews if it either performed subpopulation scenarios or extrapolated existing data to simulate the real world with respect to impacted population, disease burden, and treatment response. The attached "references" list identifies data sources for inputs that are particularly important in obesity, including:	Thank you for your comment. In our approach, we missed estimates for the patients at higher risk of obesity-related cardiovascular conditions who may potentially benefit from optimal weight management. The scope of our research centered on a general population able and willing to receive life-long weight management. While we understand that there is an increase in the risk of obesity-related conditions in certain subpopulations, we have limited ability to conduct subgroup-specific assessments unless the efficacy estimates for the specific subpopulation are available.
4.	ICER does not appear to fully consider the association between obesity and heart failure. It appears that MI risk is the driver for heart failure inputs in ICER's model despite the connection between obesity and non-MI-associated heart failure.	We acknowledge this as a limitation of our analysis. We assumed that hypertension and diabetes management would be optimal across all populations, regardless of weight management treatment. Therefore, the incremental impact of medications for weight loss on non-ischemic heart failure incidence would be expected to be minimal. In addition, there was concern about multicollinearity in the different pathways to heart failure and a considerable possibility of overestimating the benefits of medications for weight loss on heart failure.
5.	ICER limits its inputs related to Type 2 diabetes (T2D) to insulin costs and cardiovascular outcomes. Individuals of color have disproportionate prevalence and compromised outcomes associated with T2D that are ignored by ICER's model. Given the clear link between obesity and T2D, as well as the heightened risk associated with obesity for patients with T2D, ICER should include the range of T2D outcomes, as well as their associated costs and impact on quality of life, in its obesity review.	The costs and utilities included in the model for patients developing diabetes were comprehensive, including all costs and disutilities reported in the supporting publications (not just insulin and cardiovascular outcomes).
6.	ICER's model does not reflect the increase in all-cause mortality associated with obesity. Studies suggest that obesity reduces life expectancy by 9 years (Flegel 2013; Greenberg 2013) and that patients resolving their obesity can mitigate their long-term health risks (Ma 2017).	In developing our cost-effectiveness model, we sought information demonstrating decrease in all-cause mortality. The medical management strategies have not demonstrated reductions in all-cause mortality. Despite the lack of such information, our model does include changes in

	The model does not consider ongoing weight gain in patients failing behavioral interventions and not receiving anti-obesity medication or reduced effectiveness of behavioral interventions in individuals of color. Economic models generally assign utility increments and decrements for incremental decreases and increases in BMI – a range of decrements should be assigned to the base case calculations for behavioral interventions alone.	mortality that may occur as part of preventing serious cardiovascular events. Thus, in spite of the lack of such evidence, our model does permit changes in mortality brought on through the prevention of cardiovascular disease. Scenario analyses included effect of ongoing weight change over lifetime and utility associated with BMI change on the cost effectiveness, which we believe reasonably addressed the concern on the lack of BMI-trajectory related outcomes from the base-case calculation. The model did include a disutility for increased BMI, which is listed in utilities in Table 4.2.
7.	The Draft Evidence Report did not include 2021 evidence demonstrating that Semaglutide's effectiveness is similar across races and that it is especially effective in individuals on the lower-BMI levels of obesity and in female patients.	Please see prior comments and responses.
8.	The review appears to assume that ALL patients on medication will remain on drug throughout their lives. The prevailing standard of care is to continue medication ONLY in patients losing at least 5% of body weight in the initial 12 weeks (some recommendations suggest 6 months) of treatment. Including non-responders in the "averaging" is appropriate in clinical trials but not in modeling costs and benefits to mirror real-world use. We suggest that non-responders "exit" the model at 3 or 6 months.	We acknowledge that the structure of our model did not allow testing the rate of discontinuation. Using the average effect estimates from the NMA of intention-to-treat cohort data, we were able to estimate the anticipated cost effectiveness in patients eligible and willing to receive medications for long-term weight management. Although not modeled explicitly, we did include the cost of discontinued therapy in those patients who discontinued treatment initially. Since data supporting the model came from clinical trials, we did not have a good estimate of treatment effectiveness among responders only. Thus, the difference in treatment effect among responders was not modeled and is a limitation of the analysis.
9.	CDC and CMS have cited to a report compiled by The Milken Group," finding that in 2016, obesity-associated chronic conditions accounted for $480.7 billion in direct health care costs in the US, and an added $1.24 trillion in indirect costs. ICER's figures for the same year set direct medical costs at $260 billion. Moreover, the report noted that obesity is the greatest contributing risk factor to the burden of chronic diseases, accounting for $47.1% of total US chronic disease costs. While we do not assert that all those costs would be eliminated through clinically meaningful weight loss, an estimated range of avoided costs and/or improved outcomes would improve the accuracy of ICER's base case and scenario calculations and alert readers to the inherent uncertainties associated with calculating and comparing value in obesity interventions.	Thank you for the information about the specific evidence appraised in the CDC and CMS reviews. This report details the costs of conditions associated with obesity, but does not detail the impact of weight loss on these costs. While this paper may provide support for the economic importance of weight loss, these estimates are not in a format that allows their inclusion as model inputs.
10.	Clinical guidelines include cautionary statements on use of the various treatments that should be included in ICER's final evidence review, including	Thank you for your comment. In the clinical section of the Report, we describe the potential harms associated with these medications. This includes prescribing information from the FDA of particular concerns – as reflected in black

	• Phentermine should be avoided in patients with diabetes mellitus and uncontrolled hypertension or a history of heart disease (Endocrine Society, European Society of Endocrinology, Obesity Society Guidelines), a history of nephrolithiasis (AACE guidelines) or anxiety disorders • Naltrexone/bupropion, lorcaserin, and phentermine/topiramate ER are not recommended in patients with severe renal impairment (<30 mL/min) (AACE guidelines) • Medications other than naltrexone/bupropion should be used in patients with high blood pressure. Naltrexone/bupropion should be avoided in patients with chronic pain requiring opioid medications.	box warnings. The issues mentioned here include other important prescribing information. Generally, this is considered beyond the scope of an ICER Report.
11.	We appreciate ICER's previous efforts to quantify the societal value of reducing health disparities within its value framework and recommend that the HIDI include disparities in both prevalence and health outcomes. ICER has previously calculated a Health Improvement Distribution Index to acknowledge and quantify increased subpopulation health gains in disease states that disproportionately affect identifiable subpopulations. We believe that inclusion of a HIDI in ICER reviews highlights ICER's goal of reducing health disparities and inequities within its value framework. The HIDI can be a helpful tool toward that goal, particularly if ICER refines its methodology to: • Incorporate disparate prevalence among subpopulations as one factor in calculating potential health improvement. • Include consideration of greater disease burden beyond prevalence to include poorer health outcomes, higher risk of comorbidities, variability in disease progression and treatment response, differential age of onset, and other factors that contribute to health disparities and inequities.	Thank you for your comment. In its current form, the Health Improvement Distribution Index evaluates the relative potential health gains across identified subpopulations within the overall population of affected individuals in the US. As such, the Health Improvement Distribution Index helps characterize opportunities for relatively greater health gains within subpopulations that have been subject to disparities in access to care and/or health outcomes. Presently, the Health Improvement Distribution Index is calculated as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. A HIDI above one suggests that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a Health Improvement Distribution Index of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. Policymakers may wish to give greater priority to interventions that have a potential benefit of helping reduce health disparities. To keep the Health Improvement Distribution Index messaging concise, we suggest considering at most two Health Improvement Distribution Index subgroups per assessment. Further, we only consider prevalence at this time to keep the Health Improvement Distribution Index approach clear and concise as well. This may or may not be subject to change in the future.

Other

#	Comment	ICER Response
	Matthew James Wiecek	
1.	Your report shows that Lifestyle Modification leads to 16.95 QALYs. This does not pass even a basic sanity check given that it is well established in the literature that Diets and Exercise do not result in weight loss in the long term. Indeed, the control group for the STEP trials judging Wegovy's effectiveness used "Lifestyle Changes" as the control group. The STEP trials found that Wegovy significantly outperformed the control group when it came to weight loss. Your own draft report notes that Wegovy received a B+ rating due to the "demonstration of substantial short-term weight loss from multiple high-quality studies with few serious harms." How is it possible, then, that "Lifestyle Modification" (presumably diet and exercise) can result in 16.95 QALYs, when it is well established that "Lifestyle Modification" does not result in long term weight loss? How is it possible that Wegovy, which results in substantially more weight loss than "Lifestyle Modification" only results in 0.9 more QALYs than "Lifestyle Modification?" Whatever methodology was used to generate these values is clearly suspect. Quite frankly, based on the overwhelming evidence that "Lifestyle Modification" does not lead to any meaningful weight loss over the long-term, the QALYs gained from it should be 0. Any other value should be highly suspect.	QALYs are a combination of health-related quality of life (measured as a utility) multiplied by life expectancy. Therefore, the reported QALYs with lifestyle modification are those accumulated in the model over the patient's lifetime (i.e., 16.95 units). Each of the treatments resulted in a greater number of QALYs than lifestyle modification. Note that in clinical trials, medications resulted in a BMI change of between 4.6% and 13.7% of total BMI. Depending on baseline BMI, patients were still at higher risk of cardiovascular events than a cohort of patients with BMI <30 would be.
2.	In addition, "Bupropion/Naltrexone" has only a "C+" rating in your report. Yet it has a benefit of 0.33 QALYs as compared to Wegovy's net benefit of 0.9 QALYs. This also does not appear to pass the smell test. One of these has a likelihood of having a small net benefit while Wegovy has a "moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit." Surely moderate certainty of substantial net benefit should lead to substantially more QALYs than "moderate certainty of a comparable or small net health benefit." The results of the draft report appear to be so obviously defective; the entire report should be scrapped and redone. In addition, a thorough review of the current analysis should be done to figure out how, exactly, "Lifestyle Modification" could have received any meaningful amount of QALYs at all and the lessons learned should be applied to the follow-up report to ensure that the same mistake is not repeated. Obesity is one of the greatest public health threats of the last 50 years given that 70% of Americans are overweight or obese. It is	Thank you for your comment. We provide details of the reasoning behind our evidence ratings in Section 3.3. The outcomes, specifically the quantitative weight loss observed in these trials reported in this section, are used in the cost-effectiveness models.

#	Comment	ICER Response
	critical, therefore, that this ICER report gets the analysis right. If the QALY values of the draft report do not pass the smell test, it is vital we double check. If we still receive the same outcome, it is vital that we dig in and fully understand how we generated these values and fully explain to the public how "Lifestyle Modification" can lead to about equivalent QALY gains as medication that actually lead to substantial weight loss. Getting this report right is vital to both the public health and to the credibility of institutions like ICER.	
Partnership to Improve Patient Care		
1.	ICER's model assumes the burden of obesity is limited solely to CVD risk, which likely underestimates the overall benefit of intervention. Obesity is a complex disease that can lead to an impact the severity of many diseases. It can also have an independent impact on an individual's physical and social functioning and quality of life. Given this reality, any model designed to assess benefit of treatments for obesity must reflect this complexity, not treat obesity solely as a risk factor for CVD.	Please see our prior response to similar comments. In short, this analysis did not include some of the conditions and costs listed for several reasons: 1) the conditions listed in recent appraisals or previous studies would have a nominal influence on the cost and QALYs; 2) benefits of having such conditions would be captured by the estimated decrease in the cardiovascular mortality and BMI-related health utility; 3) there is insufficient evidence on the causal association between the BMI change and onset of the conditions; and 4) we were unable to properly adjust for the double-counting problems using the current model-based cost-effectiveness assessment frame, leading to overestimation of the weight-loss benefits.
2.	ICER's model ignores the benefits of treatment on physical function, which can have a significant impact on a patient's quality of life. Trials for semaglutide showed a 10-point improvement in physical function scores for patients from a baseline of around 50. This is a 20% improvement in quality of life related to physical functioning. That is likely worth 2-3 additional points in respect to health utility gains over and above any gains from reduction in CVD risk, but this value is not incorporated into the model. Given that the model assumes an overall mean QALY gain over a lifetime of just 0.25-0.89 QALYs, an additional 0.03 could be a significant addition. This benefit should be incorporated to capture a full picture of a patient's improvement with treatment. Similarly, liraglutide shows a 5-point improvement in physical function score compared to placebo, as well as a statistically significant improvement in mood and self-esteem. These are benefits also excluded from a model that is based solely on CVD risk.	A disutility associated with BMI changes and cardiovascular conditions was included and captures changes in physical function with weight gain or loss.
3.	The model's assumption about how long patients will receive treatment for obesity is unrealistic, which leads to an overestimation of treatment costs over a lifetime. The model assumes that patients will be on the drug under evaluation for 20 years. Though clinical guidelines indicate lifetime treatment, real world observation studies have	Please see our response to similar questions above. In addition, note that lifetime treatment captures both the benefits and costs of such treatment. The benefits and costs would be proportionally less, dependent on the length of treatment, with the resulting incremental cost-effectiveness ratio of treating for a shorter period of time

#	Comment	ICER Response
	suggested that patients are unlikely to continue treatment beyond 2 years. Other models similarly structured around estimating the benefits of obesity medications limited to reductions in relative risk of CVD events have tended to make this very assumption, and have produced different results, even though they have assumed weight gain once patients stop treatment happens at a faster rate than natural weight gain.	(e.g., two years) similar to lifetime treatment. In testing short-term treatment on lifetime cost-effectiveness, complete prevention rather than delay in cardiovascular events resulted in an overestimate of the benefits of the short-term treatment. It is likely that other models estimating long-term cost-effectiveness with short-term treatment suffer from this same issue.
4.	ICER's model uses data from randomized controlled trials. Real world data would be more appropriate in this scenario. Baseline cohort characteristics that act as the patient archetype in ICER's model are derived from RCTs, not from real world populations diagnosed with obesity. RCTs tend to have strict inclusion and exclusion criteria, meaning they tend to be healthier populations than real-world populations with co-existing conditions and higher health needs. Using this group to derive baseline data may underestimate the burden of disease on people with obesity and ultimately underestimate the value of the treatments being evaluated.	ICER acknowledges the value of real-world evidence. We are willing to replace current inputs with real-world evidence when robust assessment on the comparative effectiveness of anti-obesity medication is available.
5.	ICER continues to rely on the QALY, which is known to be discriminatory. Multiple studies have shown that cost-effectiveness models that use the QALY discriminate against patients with chronic conditions and people with disabilities. There is widespread recognition that the use of the QALY is discriminatory. 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. PIPC encourages ICER to heed this advice and work to develop and use better, non-discriminatory metrics.	ICER follows common academic and health technology assessment standards by using the cost per QALY gained, but also presents cost per life year gained and cost per evLY gained. The QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives and has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years.
6.	ICER uses Framingham risk equations, which are known to underestimate risk in populations of lower socio-economic status. A recent study evaluating the Framingham risk equations in groups of differing socio-economic status showed that the ratio of predicted-to-observed cardiovascular mortality for men and women with complete risk factor information was 0.56 a relative underestimation of 44%. CVD mortality was also underestimated by 48% in manual participants compared to 31% in the non-manual participants. Underestimation was also worse in participants from lower income areas. The likely consequence is that treatments are estimated being less effective than they would be for those with the fewest resources. This finding has been confirmed in other studies. PIPC would suggest that ICER carefully consider	We agree that the benefits in a subset of the population with high BMI may not be adequately captured in our model. We acknowledge this as a limitation of our analysis. The scope of our assessment includes the general population able and willing to receive life-long weight management. We acknowledge that certain subpopulations may not be well represented by the risk equations used in our model. Unfortunately, other risk equations suffer from the same issues. After a thorough review of the literature, we believe that the ACC/AHA guideline risk equation is the best available source for estimating cardiovascular risk in patients with obesity.

#	Comment	ICER Response
	this and look to alternate sources, as use of tools that do not accurately capture benefit to those in lower socio-economic classes will perpetuate existing health inequities.	
7.	To accurately capture the heterogeneity of patient populations, ICER should be producing ranges, not averages. ICER's model estimates cost-effectiveness based on average treatment effect (ATE), not incremental effect of treatment for individuals. It is well established that generating and reporting of differential value estimates across subgroups leads to substantial health gains, both through treatment selection and coverage. PIPC encourages ICER to move away from the assumption that all patients are the same, and that the value to each can be determined by the estimation of an average value only.	Thank you for your comments. We agree that there is substantial heterogeneity in the population under review. Despite the limitations of using average treatment effect, the cost-effectiveness ratio is used to make decisions about a population. Evaluating the cost effectiveness of subpopulations is only relevant when treatment decisions may be dependent on those subpopulation characteristics. As such, we evaluate different starting BMI classifications in a scenario analysis.
Paul Langley, PhD, College of Pharmacy, University of Minnesota		
1.	It is not clear from the discussion provided how these various sources were utilized to create the utilities for the parameters identified in Table 4.1. We are told (there is no additional information in the appendix) that the starting utility is from Sullivan utilizing the EQ-5D-3L for hypothetical patient characteristics and that the linear association between utility is from Pi-Sunyer where we have the SF-36 and two other instruments. These are far from informative descriptions. Perhaps more details can be provided to allay concerns? It is no good just citing references, giving no further details, and expecting the reader to follow up on the trail of references with different instruments cited. Perhaps your consultants mapped from the SF-36 to the EQ-5D-3L?	Our reporting of model inputs is consistent with previous ICER Reports and typically includes more information provided than in an academic publication. Table E4 in the Supplement contains a comprehensive listing of all model inputs. The authors may be contacted for detailed information on how the model inputs were derived from the source documents.
2.	In the case of comorbidities associated with higher BMI we are referenced to Matza for acute stroke disutility and chronic post-event health states. Health states were valued in a time trade off (TTO) valuation (which is ordinal). Three cardiovascular acute conditions were represented in the health states (stroke, acute coronary syndrome, heart failure) each of which are multiattribute composite TTOs which fail standards for fundamental measurement (value claims for single attributes). They admit states worse than death but try to create bounded negative values without recognizing the need for a true zero. Three TTO heath states were 'valued' for chronic conditions. The six health states are all multiattribute ordinal TTO scores and as such are not compatible with EQ-5D-3L and SF-36 scores. This means that the model includes values which are inappropriate when combined. All your expert group say (Pg. 45) is that: For comorbidities associated with higher BMI, we used consistent health state utility values across all evaluated treatments" with	Where possible and available, utility inputs were derived from sources using the EQ-5D. Where inputs were not available using this measure, the most appropriate source was chosen. Although different methodologies may provide variable point estimates, these estimates were further evaluated in sensitivity analyses. We disagree that these values are inappropriate when combined.

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	the health state disutilities derived from systematic reviews, prior studies and manufacturer submitted data with a multiplicative approach …used to apply health utility value changes for each of the Markov states. This far from clear with no mention made that the utilities come from different instruments/techniques. Perhaps you might care to clarify these points for each of the utilities including how you apply multiplicative techniques to different ordinal utility scores. To claim your health states have consistent utility values is incorrect.	
3.	An issue that is overlooked by Drummond et al in their characterization of the various multiattribute utility measures is the requirement that the utility score should have bounded ratio properties (a true zero and an invariance of comparisons) with normally distributed scores if they are to be summarized in terms of means and standard deviations. These are strict requirements which none of the instruments meet. The presence, by design, of health states with negative values means there is no true zero and the scores are ordinal. The question of normality is never raised, at least in all of the models your expert groups have produced over the years. If normality and bounded ratio properties cannot be demonstrated then the application of means and standard deviations is disallowed. The reason is simple: the impact of extreme values which produces extremely wide standard deviations. You have no basis for correctly supporting claims for response to therapy (or creating QALYs). All you can do with your ordinal scores is to produce medians and interquartile ranges. Given the need for normality and a bounded ratio scale, perhaps your expert modeling group could confirm that is the case for all the utilities in the obesity model?	We are unable to identify the model inputs referenced in your comment. We assume the negative values described are disutilities that do not suggest a state worse than death, but instead a disutility that could be applied to a positive utility resulting in a utility that is still positive.
4.	Given the need for normality and a bounded ratio scale, perhaps your expert modeling group could confirm that is the case for all the utilities in the obesity model? In addition, given you application of different utility measures (as I am not the only one with these concerns) perhaps your academic consultant group could allay these use of alternative utility concerns by an unequivocal statement that the utilities listed in Table 4.2 are all from the same instrument; that they are equivalent in terms of the criteria identified by Drummond et al. If the response is positive, it would be useful to detail for each of the utilities listed how this transformation from apparently diverse ordinal instrument sources was achieved? Of course, it may be that utility data were so limited that your consultants were forced to capture what they could from a diverse array of sources and for the purpose of the model assume they are equivalent without going into too	Please see above.

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	much detail. If so, this merely points to the inadvisability of assumption driven simulation	
	Thomas Kaye RPh., MBA, FASHP, K-Groups Strategies LLC	
1.	As noted in the draft document the GPL-1 are generally very costly, some injectables may offer a patient concern as to needle aversion and the oral tablets offer an alternative dose form. All the medications listed in the context of the draft publications offer side effects from mild to serious in outcomes for those patients that may seek such therapy. In some instances, the drug package inserts carry a black box warning to be heeded. Thus, is the risk of a serious and possible life threating side effect worth the treatment for a self-imposed syndrome? Secondly, when is the right time to initiate such obesity treatment; additional data analysis will need to be formulated to fully evaluate a sociological benefit in reductions healthcare costs. Some may point to impending pre-diabetes potential and frank diabetes that has followed the increase in obesity; possible complicated cardiovascular efficacy, hypertension and cancer being promoted by the medications from side effects. This alone may also stimulate costs due to unintended consequences at attempting to help. The point being that the progression of wishful desires by the manufacturers in cost avoidance dialog with reduction of future disease costs remains high in question. Its needs to be recognized that this position is not tenantable based on the cost to be incurred or increasing the dwell time for disease advancement which may be slowed with simple lifestyle changes. Prevention of disease is not always salient in deployment. The dwell time to development of disease may exceed the membership duration of the patient. Benefits are offer the member based on medical necessity, not hopeful changes. Most of the obesity seen is derived based on self-anointed-lifestyles and self-image as envisioned by the patient as to body image, not medical necessity. When the obesity reaches a point of medical complexity and known avoidance of higher costs if so used, and there is a clear view for therapy advantage as to patient cost this should implemented based on the class of obesity of I,II or III. (Medicare and Medicaid) have explicit non-coverage, non-payment regulations for obesity treatments as listed. Exclusions are also to prevent payments for “morbid” obesity as described as class (I,II,III obesity)as defined by the CDC reference. This being said payer plans do evaluate patients who are morbidly obese (greater than 32+ BMI)	Thank you for your comments. In terms of side effects, we highlight risks for each of the medications. In general, we found few serious side effects in the trials. In discussions with patients, clinicians will review the potential risks and benefits. For many individuals, the potential for weight loss and the benefits associated with this outweigh the risks of treatment, including uncommon but serious events. The decision to initiate treatment is best made between patients and clinicians. Our model considered the effects of individuals starting treatment at different baseline weights. ICER undertook this review to address the relative benefits and risks as well as the cost effectiveness of treatment. Though the cost to an individual or society may be high, if the benefits are also high, then we should seek to make these treatments accessible. Our Report supports the notion that treatment is based on medical need.

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	and may apply non-reimbursed costs for care in means of known cost avoidance of more serious disease progression with co-morbid patients. This is especially true for pediatric patients and payment stemming from (EPSDT, Early and Periodic Screening, Diagnostic, and Treatment)4 . This regulation is also implemented often to the commercial benefit member uniformly in policy. It remains that opening the door to obesity therapy would be a very significant expense to payers of the benefits without current cost offsets for future disease prevention. Until a validated financial analysis can be provided as to cost effectiveness and cost reductions in the future, the use of obesity drug should remain excluded for all but those morbid obese patients. It needs to be understood the patient is not being denied such opportunity for the drug use, but restriction as to payment for a non-covered benefit. The patient may if desired purchase the drug with a prescribers prescription with his or her personal money without payer plan sponsorship payment. Our healthcare system presently is the highest cost venue in the world, opening this therapy up offers little healthcare gain other than possible vanity for many but with a significant cost burden on stakeholders of healthcare.	