

August 8, 2022

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to provide feedback on ICER's assessment of treatments for obesity management. Obesity is a complex disease that increases the risk for other diseases and conditions. The prevalence of obesity in the United States is growing, and it is important that appropriate interventions are available to individuals that address obesity and limit risk of associated diseases. PIPC asks ICER to consider the following comments.

ICER's model assumes the burden of obesity is limited solely to cardiovascular disease (CVD) risk, which likely underestimates the overall benefit of intervention.

Obesity is a complex disease that can lead to and 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 cardiovascular disease (CVD).

There is widespread evidence that many conditions are impacted by obesity such as non-alcoholic fatty liver disease (NAFLD),¹ gallbladder disease,² sleep apnea,³ and fatigue.⁴ The global burden of disease study highlights that obesity is a significant driver of population-attributable risk in the mortality and morbidity burden of many diseases including osteoarthritis, chronic back pain, chronic kidney disease, chronic liver disease, Alzheimer's, asthma, colorectal, esophageal, pancreatic, liver and uterine cancers.⁵ It has been estimated that obesity is the cause of up to 15% of all-cause mortality in the US.⁶ The need for hip and knee replacement are also accelerated by 10-15 years in people with obesity,⁷ which leads to increased medical costs and physical burden on patients.

¹ Koutoukidis DA, Koshiaris C, Henry JA, Noreik M, Morris E, Manoharan I, Tudor K, Bodenham E, Dunnigan A, Jebb SA, Aveyard P. The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Metabolism*. 2021 Feb 1;115:154455.

² Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *Jama*. 1999 Oct 27;282(16):1523-9.

³ Jehan S, Zizi F, Pandi-Perumal SR, Wall S, Auguste E, Myers AK, Jean-Louis G, McFarlane SI. Obstructive sleep apnea and obesity: implications for public health. *Sleep medicine and disorders: international journal*. 2017;1(4).

⁴ Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *The Journal of Clinical Endocrinology & Metabolism*. 2000 Mar 1;85(3):1151-8.

⁵ <https://www.healthdata.org/data-visualization/gbd-compare>

⁶ Flegal KM, Panagiotou OA, Graubard BI. Estimating population attributable fractions to quantify the health burden of obesity. *Annals of epidemiology*. 2015 Mar 1;25(3):201-7.

⁷ Changulani M, Kalairajah Y, Peel T, Field RE. The relationship between obesity and the age at which hip and knee replacement is undertaken. *The Journal of Bone and Joint Surgery. British Volume*. 2008 Mar;90(3):360-3.

With obesity having such a broad range of health ramifications, representing the burden of obesity as a risk factor for CVD and CVD events is over-simplistic and likely to underestimate the net health gain from appropriate treatment.

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 50.⁸ 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.

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 suggested that patients are unlikely to continue treatment beyond 2 years.⁹ 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,¹⁰ 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.¹¹

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 randomized controlled trials (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

⁸ Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MT, Wadden TA, Wharton S. Once-weekly semaglutide in adults with overweight or obesity. *New England Journal of Medicine*. 2021 Feb 10.

⁹ Ganguly R, Tian Y, Kong SX, Hersloev M, Hobbs T, Smolarz BG, Ramasamy A, Haase CL, Weng W. Persistence of newer anti-obesity medications in a real-world setting. *Diabetes research and clinical practice*. 2018 Sep 1;143:348-56.

¹⁰ Kim, Nina, Jessie Wang, Chakkarin Burudpakdee, Yan Song, Abhilasha Ramasamy, Yanwen Xie, Rochelle Sun, Neela Kumar, Eric Q. Wu, and Sean D. Sullivan. "Cost-effectiveness analysis of semaglutide 2.4 mg for the treatment of adult patients with overweight and obesity in the United States." *Journal of Managed Care & Specialty Pharmacy* 28, no. 7 (2022): 740-752.

¹¹ Ara R, Blake L, Gray L, Hernandez M, Crowther M, Dunkley A, Warren F, Jackson R, Rees A, Stevenson M, Abrams K. What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review. *Health Technology Assessment (Winchester, England)*. 2012;16(5):iii.

baseline data may underestimate the burden of disease on people with obesity and ultimately underestimate the value of the treatments being evaluated.

ICER continues to rely on the Quality-Adjusted Life Year, which is known to be discriminatory.

Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions¹² and people with disabilities.¹³ 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.¹⁴ PIPC encourages ICER to heed this advice and work to develop and use better, non-discriminatory metrics.

ICER uses Framingham risk equations, which are known to underestimate risk in populations of lower socio-economic status.

A recent study¹⁵ 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.¹⁶ PIPC would suggest that ICER carefully consider 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.

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.¹⁷ It is well established that generating and reporting of differential value estimates across subgroups leads to substantial health gains, both through treatment selection and

¹² Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.

¹³ Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.

¹⁴ https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf

¹⁵ Brindle PM, McConnachie A, Upton MN, Hart CL, Smith GD, Watt GC. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. British Journal of General Practice. 2005 Nov 1;55(520):838-45.

¹⁶ Ramsay, S.E., Morris, R.W., Whincup, P.H., Papacosta, A.O., Thomas, M.C. and Wannamethee, S.G., 2011. Prediction of coronary heart disease risk by Framingham and SCORE risk assessments varies by socioeconomic position: results from a study in British men. *European Journal of Preventive Cardiology*, 18(2), pp.186-193.

¹⁷ Stevens W, Normand C. Optimisation versus certainty: understanding the issue of heterogeneity in economic evaluation. Social science & medicine. 2004 Jan 1;58(2):315-20.

coverage.^{18,19} 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.

Conclusion

PIPC encourages ICER to make changes in its model to ensure it is representative of a real-world population, including using real world evidence where possible and recognizing the broad implications of obesity beyond risk of CVD.

Sincerely,



Tony Coelho
Chairman
Partnership to Improve Patient Care

¹⁸ Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. *Journal of health economics*. 2011 May 1;30(3):549-59.

¹⁹ Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. *Medical Decision Making*. 2014 Nov;34(8):951-64.