CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

Controversies in Obesity Management

Summary of Public Comments and Response on Draft Report

June 23, 2015

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Response to Public Comments

The Institute for Clinical and Economic Review (ICER) produces publicly-available evidence reviews for consideration by the California Technology Assessment Forum (CTAF) and the New England Comparative Effectiveness Public Advisory Council (CEPAC). As part of this process, ICER welcomes public comment from individuals and organizations on its proposed project scope, voting questions, and evidence assessment. For transparency, all those submitting comments during the public comment period are acknowledged in this response document. However, detailed responses are focused on those comments pertaining to the project scope, evidence assessment, and major assessment findings. Comments related to program decisions, process, or other matters not pertaining specifically to the draft key questions, project scope, or evidence assessment are acknowledged through inclusion only.

This document responds to comments from the following parties:

- **Matthew L Maciejewski, PhD**, Professor, Department of Medicine, Duke University / Research Career Scientist, Center for Health Services Research in Primary Care, Durham VA Medical Center, Durham NC
- **Jamie Ponce, MD, FACS**, Medical Director, Bariatric Surgery Program, Hamilton Medical Center, Dalton, GA and Memorial Hospital, Chattanooga, TN
- **Sajani Shah, MD**, Surgeon, Department of Bariatric and Minimally Invasive Surgery, Tufts Medical Center / Assistant Professor, Tufts University School of Medicine, Boston, MA
- **Medra Pattillo,** patient, Fairfield, CA
- **Katherine Tweden, PhD**, Senior Vice President, Research, EnteroMedics, St. Paul, MN
- **Erica Roy-Nyline**, vBloc Patient, St. Paul, MN
- **Mike Magnant**, vBloc Patient, Carver, MA
- **Scott A Shikora, MD, FACS**, Executive Vice President and Chief Medical Officer, EnteroMedics, Boston, MA
- **Randi Fain, MD, FCCP**, Group Director, Medical Strategy, Specialty Care, Medical & Scientific Affairs, Eisai, Inc., New York, NY
- **Laura LeBoeuf, MS**, Vice President, Quality, Regulatory, and Clinical Affairs, Apollo Endosurgery, Austin, TX
- **Steve Chen, MD**, Executive Medical Director, US Medical and Scientific Affairs, Takeda Pharmaceuticals International, Chicago, IL
- **Todd Hobbs, MD**, North America Chief Medical Officer, Novo Nordisk, Inc., Plainsboro, NJ
- **Louis J Aronne, MD, FACP**¸ Sanford I Weill Professor of Metabolic Research, Weill-Cornell Medical College / Vice Chairman, American Board of Obesity Medicine, and **Rekha B Kumar, MD, MS**, Assistant Professor of Medicine, Division of Endocrinology, Diabetes and Metabolism, Weill-Cornell Medical College, Comprehensive Weight Control Center, New York, NY
- **Todd Andrew Kellogg, MD**, Surgeon, Mayo Clinic, Rochester, MN
- **John B Dixon**, MBBS, PhD, FRACGP, FRCP, Head of Clinical Obesity Research, Baker IDI Heart and Diabetes Institute, Melbourne, Australia

Comments on CTAF Draft Report		
	Comment	**Response**
Matthew L Maciejewski, PhD, Professor, Department of Medicine, Duke University / Research Career Scientist, Center for Health Services Research in Primary Care, Durham VA Medical Center, Durham NC		
1	ES5: In the statement of "moderate certainty of a substantial net health benefit of bariatric surgery", it would be helpful to state which procedures appear to provide the greatest net health benefit for patients with a BMI of 35 and above. That would be consistent with the qualification provided in the summary for patients with BMI 30-34.9.	Thank you for your comments and references. Discussion of overall net health benefit according to procedure type for patients with a BMI ≥35 has been added to the Executive Summary and Evidence Review sections.
2	Pages 30-31: Clearly state the duration of follow-up for Figures 8 and 9. In the discussion and the figures themselves, the meta-analytic results do not state the duration of follow-up for these pooled treatment effects. It is critical to qualify the duration of follow-up in each trial in Figures 8 and 9, so the reader has a clear sense of how little evidence there is for weight loss beyond 2-3 years.	We added a footnote for Figures 8 and 9 stating that follow-up in these studies ranged from 1-2 years. We also added clarifying language in the section assessing the impact of bariatric surgery on weight loss to indicate that evidence beyond a median of two years of follow-up is lacking.
3	Page 41: The discussion of procedure volume and its association with patient outcomes fails to report results by Dimick and Nicholas published in JAMA (Feb 2013; Oct 2013) showing that center of excellence designation, which is partly related to patient volume, showed no difference in outcomes. Those results are important to include, since CMS reversed its coverage policy regarding centers of excellence in part based on these results.	Thank you for the references. We added a brief discussion of accreditation and the basis for the reversal of CMS's certification requirement in the section on volume. Dimick 2013 and a few other key studies that formed the basis of the CMS decision are now cited.
4	Page 67: The discussion of the Padwal 2011 systematic review does not examine the specific studies underlying that review, several of which use matched controls that conducted matching in a profoundly flawed way. That is, several studies (Cremieux, Finkelstein) matched surgical patients to non-surgical controls on the basis of pre-surgical expenditures, which were accelerating in the 12 months prior to surgery due to pre-surgical work-up or emergent issues that put the future surgical patients on the path to bariatric surgery. Non-surgical controls with similar pre-surgical "spikes" are likely not generalizable to eligible non-surgical controls, but represent outliers in their pre-surgical expenditure trends and, more importantly, not generalizable in their post-surgical expenditure trends. In sum, matching on pre-surgical expenditures set up a false comparison that ended up making expenditures of bariatric patients look better in comparison than they might have in the absence of matching on pre-surgical expenditures. This is a subtle point that would benefit from empirical verification in a general US population, but I am (almost) convinced that this must be true.	The Padwal systematic review includes neither the Cremieux nor the Finkelstein studies. We have added clarifying language describing variability in economic study design, perspective, and setting, however.
5	Page 68: It would be worth noting in the summary of the Weiner 2013 paper that only 10% of the original study sample was followed out to 6 years.	We have made this clarification in the revised draft report.

6	Page 68: I was surprised that this review of the literature did not reference the 2012 Archives of Surgery by my colleagues and I published. While expenditure analyses on veterans may not generalize to non-VA populations, it should be mentioned given that restriction to non-veterans did not appear to be an inclusion criteria.	We have added a discussion of this paper to the revised draft report.
7	Page 68-69: Further, there were two commentaries about the lack of cost savings in bariatric surgery (Maciejewski and Arterburn, 2013 JAMA; Goldfine, Vernon and Zinner 2014 JAMA Surgery) that may merit summarizing as well.	Because these commentaries do not include additional original research data, they are not summarized but instead added for further context.
8	Simulation Model: The cost-effectiveness results to 10 years hinges critically on the assumption of the decrease in expenditures per unit of BMI decrease (3%, page 76). This assumption should be subject to sensitivity analysis, given that Neovius (2012 JAMA) and Weiner (2013 JAMA Surg) found that expenditures did not decline over time at a 3% rate per unit of BMI decrease and appeared to plateau. A range of scenarios should be assessed in terms of how quickly cost reductions plateau and the percentage reduction per unit of BMI decrease. I would guess that results are highly sensitive to these two assumptions that are not clearly stated in the decision model assumption section.	Results were not overly sensitive to variation in the assumed decrease in expenditures per unit of BMI decrease. We ran several analyses where we varied this parameter. These are reported in the Tornado diagram in Figure 13 of the draft report. When we assumed cost did not change per unit of BMI decrease, the incremental cost-effectiveness ratio for RYGB vs. standard care using a 10 year time horizon increased to $46,629. The ratio decreased to $22,376 when we applied a 5% decrease in cost per unit of BMI decrease. Assumptions regarding a plateau effect, while not formally investigated, would fall somewhere in between these values.
Jamie Ponce, MD, FACS, Medical Director, Bariatric Surgery Program, Hamilton Medical Center, Dalton, GA and Memorial Hospital, Chattanooga, TN		
1	The main focus of these comments is my concern that the review is too focused on a backward looking metric of absolute weight loss, to the exclusion of medically relevant weight loss consistent with patient's goals and objectives. The goal of this meeting – and other similar technical reviews – should NOT be an exercise in determining which diet, drug, device or surgery holds the promise of the most absolute weight loss, but rather, <u>what</u> mechanisms of action of those diets, drugs, devices and/or surgeries are most appropriately applied to <u>which</u> patients that hold the highest likelihood of being the most effect treatment for their individual cause of obesity at the lowest acceptable level of risk.	Thank you for your comments. Our review focused on weight loss as the common measurement tool employed in studies of these disparate interventions, but we also summarized data on measures of interest specific to each type of intervention (e.g., %EWL and comorbidity resolution for surgery, 5% or 10% of total weight loss for medications).
2	It needs to be understood and acknowledged that Obesity is a "chronic disease" that will always need treatment tools to manage it at different degrees of severity. People that suffer from overweight (BMI 25-29) may be treated with diet, exercise, and even medications. Other people suffering from more severe obesity (BMI over 35) might be more clear	We added clarifying language referring to obesity as a chronic disease requiring long-term management. As stated in the Executive Summary, we acknowledge that there is a level of uncertainty for treating individuals at lower levels of

	candidates for some type of surgical procedure. But there is a gap of treatment modalities for many patients in the moderate obesity category (BMI 30-40) that have exhausted the non-surgical options and are equally not quite ready for surgical treatments. Many of the endoscopic temporary modalities might have a beneficial effect to continue the treatment for these patients. So, not one therapy fits all patients and we need more tools to decide what is best for each individual case. Each of the treatments reviewed at this meeting – alone or in conjunction with one another – has a place in my treatment armamentarium to provide medically meaningful weight loss. Each treatment, when properly applied, can arrest the upwardly trending weight gain of the morbidly obese, in most cases reverse the trend and reset the patient's weight at a healthier level. With proper treatment, most of my patients will experience fewer of the co-morbid effects of obesity – resulting in lower costs for the patient and the healthcare system through fewer drugs being prescribed to treat diabetes, high cholesterol and congestive heart failure, lower risks for cancer as well as the need for fewer new knee and hip replacement implants.	BMI (i.e., 25-35 kg/m^2) that poses challenges in understanding the appropriate treatments and relevant candidates along the treatment continuum. We have also added some context around this point in Background section. It is not our intention to make specific recommendations for the most appropriate treatment (or sequence of treatments) for individual patients with obesity, but rather to present the current state of the evidence for various treatment options. We recognize that some therapies might have specific benefits based on patients' individual circumstances.
3	What concerns me the most in my read of the "Scoping Documents" for this Review that all of the procedures, whether existing, newly approved or still investigational, are being measured against "absolute weight loss" instead of examining the resolution of comorbid conditions or even just quality of life. My patients do not succeed if the outcome doesn't include fewer diabetes drugs, a lower risk of cardiovascular events, increase employability, or reduced cancers – all improvements coming with an acceptable risk/reward consideration.	Please see the response to comment #1 above.
4	The traditional "dollars-per-pound lost" measure used by Payors as a surrogate measure of efficacy has no place in this critical analysis. Sound medical management of obesity requires a realistic, achievable patient outcome that is focused on the health effects of the treatment and not just the total weight loss.	We are unsure of what is meant by "dollars per pound lost". If the comment refers to our economic analysis, we note that our estimates of quality-adjusted life years (QALYs) reflect a holistic attempt to assess the impact of all clinical effects of treatment, including weight loss, comorbidity resolution, and improved quality of life.
5	Obesity treatment must be considered dynamic, and the Scoping Document at first read fails that test by appearing too static in its review and too focused on surrogate markers of absolute weight loss versus comorbid resolution of the diseases of obesity. By telling a patient that obesity treatment was about how many pounds you can lose as opposed to how much healthier you can become, we failed to treat the	We did not prioritize outcomes for the various management options for obesity. Our intention was to present overall clinical effectiveness based on the commonly-assessed metrics of treatment success for these interventions, including weight loss and

	disease. CTAF/ICER has the opportunity to relook at obesity treatments with a different approach – one that accepts the new technologies alongside the existing procedures. No two patients are alike, no one treatment works for every patient and there are no silver bullets. CTAF/ICER should support each of the reviewed treatment options for the right patient, at the right time for the optimal outcome as determined by their physician and their own long-term goals.	improvement/resolution of comorbidities, as quantified in the scientific literature. Nevertheless, we recognize and describe the short-comings of many of the available studies, including inconsistencies in how these data are reported (e.g., %EWL vs. absolute weight loss, resolution vs. improvement of comorbidities). See comment #2 above.
Sajani Shah, MD, Surgeon, Department of Bariatric and Minimally Invasive Surgery, Tufts Medical Center / Assistant Professor, Tufts University School of Medicine, Boston,		
1	As a bariatric surgeon and clinician, I am experienced with, and use all of the approved techniques and treatments under discussion at this meeting. I am concerned in my review of the "Scoping Documents" for this Review that all of the procedures – both traditional, newly approved and those still in the FDA pipeline – are being measured against an out-of-date and decidedly non-medical standard of "absolute weight loss."	Thank you for your comments. See comments in response to Dr. Ponce above.
2	The financial analysis in the Scoping Document appears to further cloud a medical analysis by adopting a "dollars-per-pound lost" paradigm that does not reflect sound medical management of obesity, does not promote realistic patient outcome of treatment goals nor is it an appropriate intervention evaluator when physicians must determine how to treat the multi-factorial disease of obesity.	See comments in response to Dr. Ponce above.
3	The treatment paradigm of obesity has been – and appears to be repeated here – as a "one-size-fits-all" approach that places maximal weight loss as the ultimate clinical outcome. While aesthetic weight loss has it place, as a stand-alone goal, it has become obsolete. As a bariatric surgeon, I strive to work individually with each of my patients to design a treatment plan that will provide for sustained, medically meaningful weight loss. My objectives for my patients are improved cardiovascular function, lowered HbA1c, and LDL, an increased capacity for physical activity with correspondingly lowered impact on hips and knees. No solitary treatment will, by itself solve my patient's obesity each therapy requires a commitment by the patient to post-operative medical management, life style modification supported by experienced clinicians.	See comments in response to Dr. Ponce above.
4	[…] [W]e require enhanced treatment options with different reward/risk paradigms, different mechanisms of action to align with different patient disease states and interventional	See comments in response to Dr. Ponce above.

	approaches whose outcomes are focused on the expanded paradigm of medically meaningful weight loss.	
5	vBloc has been demonstrated to have an enhanced safety profile when compared to traditional bariatric surgical methods, while patients that used the device per the clinical protocol lost approximately 28% of their excess weight at 12 months, and that weight loss has been maintained through reported 24 and 30 month time periods, thereby providing an additional, novel alternative that I can offer my obese patients who are in need of treatment options.	We focused attention on published, peer-reviewed studies for the evidence review. As data from 24- and 30-month time periods have not yet been published in a peer-reviewed journal, they were not considered in our review.
6	What concerns me the most about the design and construct of this review is that ICER traditional relies on long-term, peer-reviewed, published clinical data to issue a supportive rating. It is not a system that is well-designed for the evaluation of newer, evolving technologies. vBloc, a promising technology that is working for my patients, is such a technology that has been recently approved by the FDA – January 14, 2015. It is premature for CTAF/ICER to form definitive conclusions on vBloc's durability and effectiveness, as outlined in the scoping documents, based on currently available data. But it is equally true that it is equally premature for CTAF/ICER to reach a negative conclusion based on the lack of published long term data due to the very recent regulatory approval for commercial use of vBloc. The most appropriate outcome for the CTAF/ICER evaluation is to accurately note the strong safety profile of vBloc with its promise of medically relevant weight loss, acknowledge that it is a new device awaiting the publication of longer term data. It would also appear prudent for CTA/ICER to recognize that vBloc is a technology with promise when targeted to appropriate patient populations.	While we understand that there may be concerns regarding a disconnect between the pace of innovation and journal review timelines, we have equal (if not more substantial) concerns regarding conference proceedings, press releases, and other unpublished data as sources of critical information on effectiveness and harm. While the peer review system is not without its flaws, it represents an approach to adjudication and data interrogation that does not exist with other forms of publicly-available information.
Medra Pattillo, patient, Fairfield, CA		
1	The thing I most like about this (vBloc) tool is that it puts me in control instead of hunger. When you are not constantly thinking about eating and being hungry you can focus on being healthy and mindful. That one shift makes it possible to set and reach goals in relation to nutrition and exercise. I now feel empowered and in control and able to reach my goals. I still have a way to go on my journey but I know I will reach my goal and maintain it.	Thank you for your comments. No changes were made to the draft report.
Katherine Tweden, PhD, Senior Vice President, Research, EnteroMedics, St. Paul, MN		
1	• Table ES1: "Strength of Evidence by BMI Category" indicates that there is no certainty of the evidence that vBloc is effective in the 35 to 39.9 BMI category. • The ReCharge study did assess this BMI range and an abstract has recently been accepted for oral presentation at the 2015 international federation for	Thank you for your comments. As noted in comment #6 above, we did not include any data from grey literature in the evidence review. Since data from the provided abstract have not been published in a peer-reviewed journal, they were not considered in our review.

	Surgery for Obesity (IFSO) meeting in Vienna, Switzerland. Data from 53 patients with BMI 35 to 40 kg/m^2 demonstrated 34%EWL at 12 months with no device-related serious adverse events. Statistically significant improvements were observed in systolic blood pressure, total cholesterol, triglycerides, blood glucose and heart rate (see attachment 1).	
2	• Pages ES6 and ES7 summary of Vagus Nerve Block (Maestro) summarizes the state of evidence of vBloc. The following comments regarding that summary are relevant to Draft Document discrepancies and misstatements: • Note that the first RCT conducted, the EMPOWER Trial, evaluated an earlier generation device and provided supporting evidence of primarily safety of vBloc therapy only. Efficacy was confounded by inconsistent hours of therapy delivery and an unintended therapeutic effect in the control group from electrical impedance and safety checks. The lack of evidence of effectiveness in this study needs to be considered in this context in addition to the fact that the device evaluated in the EMPOWER Trial was an early generation Maestro RF System and not the FDA approved Maestro Rechargeable System. • While outcomes related to improvements in comorbidities have not been published to date, data through 2 years are in the process of being reviewed by The Obesity Society for the 2015 meeting in November (see attachment 2). Those data demonstrate 21%EWL with systolic blood pressure (BP), diastolic BP, and resting heart rate reductions from baseline of 5.5mmHg, 3.0mmHg, and 4.4 bpm, respectively. Waist circumference reduced by 8.4cm from baseline and 50 and 47% of subjects with pre-diabetes and metabolic syndrome at baseline, respectively, no longer had those conditions at 2 years. Improvements in Impact of Weight on Quality of Life-lite questionnaire and all factors of the three factor eating questionnaire were also observed. Clearly, a clinically meaningful weight loss was maintained that resulted in improvements in comorbid conditions and quality of life. • A statement is made that 3.4 to 4.4% of patients experienced serious complications related to the device, implantation, or revision. The primary safety endpoint, which was the serious adverse event rate related to the implant/revision procedure, device or therapy in the EMPOWER and ReCharge Trials was	We have specified in our revised draft report that the EMPOWER trial evaluated an earlier generation device and mention that the seemingly minor level of charge delivered to patients in the control group may have had an effect on vagal function. As noted in comment #6 on page 8 above, we did not include any data from grey literature in the evidence review. Since data showing improvements in comorbidities have not been published in a peer-reviewed journal, they were not considered in our review. The serious adverse event rate has been corrected to 3.0-3.7% in the revised draft report.

	3.0% and 3.7%, respectively. Importantly, these events did not cause life-threatening serious complications similar to what is observed with traditional bariatric surgery such as anastomic leak, bleeding and bowel obstruction and were events such as neuroregulator site pain requiring neuroregulator repositioning within the subcutaneous pocket, atelectasis, neuroregulator revision due to malfunction not causing harm to the patient (which became serious due to investigator decision to keep the patient in the hospital overnight), gallbladder surgery and emesis requiring a hiatal hernia repair.	
3	• We also do not agree with the statement "that there was a not-inconsequential rate of device removal." Only two patients in 162 randomized to the vBloc group in the ReCharge trial had their device removed for an adverse event (one with pain at the neuroregulator site and one with heartburn). The other 3 patients left due to subject decision, but not for complications or adverse events, which is always their right to do in a clinical trial setting. • The statement that there is a small net benefit for the vBloc device compared to sham device needs to be qualified with the unexpected high weight loss response observed with the sham device. That response was deemed to be likely related to the placebo effect of surgery, daily self-monitoring reinforced by interaction with the sham device to recharge the battery and participation in the weight management program. Importantly, the sham was found to not be durable and patients gained back 40% of what they had lost at 12 months by 18 months post-implantation. Even with these factors, weight loss was superior in the vBloc group to sham control at every visit post-implant and the weight loss observed in the vBloc group is clinically meaningful. Lastly, the sham is not a therapy and cannot be prescribed. It was custom designed specifically for the ReCharge Study. • The ReCharge Study did evaluate patients with a BMI < 40 as described above. Those patients had a greater %EWL than the higher BMI patients.	The phrase "there was a not-inconsequential rate of device removal" was removed from page 54, though we note that the ReCharge trial publication states that three patients in the vBloc group had the device removed due to an adverse event (pain at the neuroregulator site, pain with therapy, and heartburn), while two patients asked to have it removed. We do not agree that any such qualification need be made. The purpose of controlled study is to account for placebo effects to ensure the most accurate attempt to ascribe incremental clinical benefit to the treatment itself. Without additional data and other comparisons available, the impact of the sham device in this study relative to other potential comparators is unknown. Results of the ReCharge study were not stratified by BMI subgroup in the published paper. Thus, we only report aggregate %EWL.
4	3. On page ES10, the statement was made that "device removal for AEs or other reasons are not uncommon." This statement is misleading. Of fact, only 2 of 162 patients in the vBloc group had their devices removed due to an adverse event, yielding a "device removal" rate of 1.2%.	The phrase "device removal for AEs or other reasons are not uncommon" has been removed from page ES10.
5	The statement of a "small net benefit of vBloc over sham" needs to be put into its proper context of 1) an uncommon	Please see our response to comment #3 above.

	sham surgery, 2) a "fully functioning" sham device and 3) a very active sham effect. Lastly, as the vBloc neurometabolic therapy patients achieved almost exactly the pre-trial specified weight loss of 25% EWL (24.4% ITT observed/26.1% multiple imputation model), the context of the sham was to ensure the therapeutic level of treatment reached clinical meaningfulness. At a p-value of .002, superiority of weight loss was demonstrated and the achieved weight loss was identical to the pre-specified trial design assumption.	
Erica Roy-Nyline, vBloc Patient, St. Paul, MN		
1	vBloc has helped me achieve the weight loss of a bariatric intervention without "going that far". vBloc gives me the appetite control and satiety of a medication without chemicals and side effects.	Thank you for your comments. No changes were made to the draft report.
Mike Magnant, vBloc Patient, Carver, MA		
1	I am now 63 years old and I can see much further into the future. Because of my weight loss with vBloc I am looking forward to a longer and healthier life.	Thank you for your comments. No changes were made to the draft report.
Scott A Shikora, MD, FACS, Executive Vice President and Chief Medical Officer, EnteroMedics, Boston, MA		
1	It is our position that the evidence for comparative clinical effectiveness for vBloc neurometabolic therapy fits into the "promising, but inconclusive category" established by ICER. This view is based on the clinically meaningful weight loss demonstrated at 12 months of 24.4% (intent-to-treat analysis) and 26.1% (multiple imputation model), combined with the low rate of related serious adverse events (all which were resolved with no sequelae). Data on weight loss and safety have been published on the trial results through 18 months from the pivotal study ReCharge. Data is in the process of being published on improvements in obesity risk factors, quality of life and longer duration safety and effectiveness in patients with a BMI between 35 and 45 kg/m^2. These data continue to support the promise of vBloc neurometabolic therapy as a durable, less invasive and safer option compared to bariatric surgical interventions.	Thank you for your comments. Given that only one RCT has been performed on the current-generation device, it would be very unusual to upgrade our certainty in the evidence to "moderate", which is required for a "promising but inconclusive" rating.
2	The second trial which provides support for the safety and efficacy of vBloc is VBLOC-DM2 which was a prospective, open-label, multi-center trial evaluating 28 subjects with obesity, type 2 diabetes and a BMI of 30 to 40 kg/m^2. This trial evaluated the Maestro Rechargeable System, where power is delivered from an internal battery and external components were used to recharge the device a few times per week. Data to 36 months post-implantation have been published. This study has shown approximately 24%EWL through 36 months post-implant with related SAEs of pain at the neuroregulator site and device malfunction. As with the EMPOWER study, these SAEs were not life threatening nor did they require emergency operation. Importantly, patients reduced their	This study was a single-arm evaluation. As stated in the "Methods" section of the report, noncomparative studies with fewer than 50 patients were excluded from our analysis.

	baseline HbA1c by 1 percentage point at 12 months and maintained a drop of 0.6 percentage points at 3 years. Similar improvements in fasting plasma glucose were also observed. Significant reductions in waist circumference of 11 and 7 cm were observed at 12 months and 36 months, respectively.	
3	Results of the ReCharge trial at the 18-month time point provide important context for weighing the benefits and risks of vBloc therapy. First, the trial continues to demonstrate sustained weight loss with vBloc therapy. vBloc appears to have a favorable safety profile with a low risk of serious complications, and non-serious complications were typically mild or moderate sensations of the therapy that were resolved with little to no intervention. Interestingly, weight loss in the Sham group was considerably diminished within 6 months of the 12-month endpoint, despite continued blinding of the study past the 12-month visit and ongoing weight management counseling.	As noted previously, we did not include any data from grey literature in the evidence review. Since data from the 18-month time period have not been published in a peer-reviewed journal, they were not considered in our review.
Randi Fain, MD, FCCP, Group Director, Medical Strategy, Specialty Care, Medical & Scientific Affairs, Eisai, Inc., New York, NY		
1	*CTAF draft report suggesting lack of evidence for lorcaserin in patients with common obesity-related comorbidities:* In the BLOOM and BLOSSOM phase 3 trials a significant number of subjects [BLOOM (45.5%) and BLOSSOM (42%)] did have comorbid conditions. The majority had dyslipidemia (33.3% and 27.7%, respectively), followed by hypertension (21.3% and 23.6%, respectively), sleep apnea (4% and 4.3%, respectively), glucose intolerance (1% and 1.5%, respectively) and CV disease (0.3% and 1.1%, respectively). Patients with hypertension were only excluded if they had persistent, uncontrolled hypertension. In addition, BLOOM-DM was a 1-year study in adult patients with BMI greater than or equal to 27 kg/m^2 with the comorbidity of inadequately controlled type 2 diabetes (HBA1C range 7-10%). Patients also had other co-morbid conditions present at baseline, primarily hypertension (34.6%) and dyslipidemia (34.8%).	Thank you for your comments. We did not intend to suggest that there is a lack of evidence for lorcaserin in patients with common obesity-related comorbidities, but rather, a lack of reporting on outcomes related to improvement/resolution of such comorbidities. As such, we have clarified the report language to prevent further confusion.
2	*CTAF report suggesting lack of evidence to support use of lorcaserin in patients with BMI<35 or ≥40:* We are puzzled by the CTAF report's statement since another section of the draft report has clearly evaluated the weight loss effect of lorcaserin in those BMI categories and concluded that "Outcomes did not differ for patients in any BMI category for either the lorcaserin or placebo groups."	We have changed the language in the summary paragraph on page 60 from "we found no evidence…" to "we found a single study that stratified outcomes according to various BMI subgroups."
3	*CTAF reporting suggesting lorcaserin is not recommended for patients with cardiovascular disease:*	This has been corrected in the revised draft report.

	We believe this is a misunderstanding of the Endocrine Society Clinical Practice Guidelines which actually recommend the use of lorcaserin or orlistat in patients with cardiovascular disease, as seen in section titled 'Care of the patient who is overweight or obese': "In patients with cardiovascular disease who seek pharmacological treatment for weight loss, we suggest using medications that are not sympathomimetics such as lorcaserin and/or orlistat."	
4	*CTAF report suggesting lack of long-term data for lorcaserin:* The BLOOM study was a 2-year study that enrolled 3182 patients. In Year 2, placebo patients were continued on placebo and lorcaserin patients were re-randomized in a 2:1 ratio to continue lorcaserin or to switch to placebo. Among patients in the lorcaserin group who had weight loss of 5% or more at year 1, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 than in those who were reassigned to receive placebo. Patients who received lorcaserin in years 1 and 2 had a lower mean body weight than patients who received placebo in both years and those who received lorcaserin in year 1 then placebo in year 2.	We maintain that there is a lack of long-term data for lorcaserin, as none of the included studies reported outcomes beyond two years (i.e., our definition of "long term"). Nevertheless, we have clarified that the BLOOM trial (Smith, 2010) followed patients for *two* years and included the following: "In the BLOOM trial, a greater proportion of patients who continued to receive lorcaserin maintained 5% or more weight loss in year 2 than those who were reassigned to receive placebo (67.9% vs. 50.3%, p<0.001)."
5	In addition, recently published post-hoc analyses of the lorcaserin pivotal trials may help further elucidate the benefit of lorcaserin as used in real-world clinical practice. The lorcaserin prescribing information indicates that lorcaserin should be discontinued if 5% weight loss is not achieved by week 12 (W12). Therefore, the benefits of lorcaserin should be evaluated based upon its use only in those individuals who demonstrate an early (W12) response, as is recommended in the prescribing information. In the pooled BLOOM and BLOSSOM trials (Completers Population) lorcaserin-treated W12 responders achieved a mean percent weight loss from baseline of 10.8% at Week 52.7 In the BLOOM-DM trial (Completers Population), lorcaserin-treated W12 responders had a mean percent weight loss from baseline of 9.1% at Week 52.	While we understand that there is specific guidance around the use of lorcaserin and other weight-loss medications in clinical practice, the standard approach in evaluating treatment effects in systematic reviews is to focus attention on specified *primary outcomes in intent-to-treat analyses* in order to provide a population-based view on treatment effects (i.e., to assess overall outcomes in those responding and not responding to treatment). However, we do also report on measures of "treatment success" – for example, those achieving 5% or 10% weight loss.
Laura LeBoeuf, MS, Vice President, Quality, Regulatory, and Clinical Affairs, Apollo Endosurgery, Austin, TX		
1	With regards to the LAP-BAND®, please include data from the 3-year U.S. pivotal study submitted to the FDA to expand the indication for use to include obese individuals with BMI 30-34 with medical comorbidity. An additional 2 years of follow-up on this same study population, culminating in 5 years of follow-up data (ClinicalTrials.gov NCT 00570505) demonstrated that >76.9% of subjects achieved at least 30% excess weight loss by month 4 and at every subsequent time point in the 5-year study.	Thank you for your comments and references. As stated in the "Methods" section of the report, we did not use case series data to assess clinical effectiveness. In addition, we did not include any data from grey literature in the evidence review.

	Pending publications include data from two FDA-regulated studies that demonstrate the rate of LAP-BAND® removals without replacement has significantly decreased since the original FDA approval for morbid obesity due to improvements in the device, procedure, and aftercare. Fifty-four months after LAP-BAND® placement, in the 5-year Lower BMI study, the rate of explants without replacement was 5.4%. Three-year and partial 4-year data from the HERO Study, an ongoing 5-year U.S. post-marketing study, has also demonstrated a 6.3% removal without replacement rate.	As previously noted, we based our evidence review on peer-reviewed publications.
2	With regards to Intragastric Balloon (IGB), FDA-PMA approval of the OBERA™ Intragastric Balloon is imminent. The U.S. pivotal ORBERA™ trial was recently presented at Digestive Disease Week (DDW) on 5/18/15 by Dr. Barham Abu-Dayyeh from the Mayo Clinic. In this multi-center, prospective, randomized, non-blinded comparative study of obese patients with BMIs 30-40, subjects were randomized to either treatment with ORBERA™ or behavioral modification alone (Control). One hundred sixty (160) patients underwent endoscopic placement of ORBERA™. The Orbera group experienced a mean 10.5% total body weight loss (TBWL) at 6 months (time of device removal), as compared to the mean 4.7% TBWL in the Control Group. The ORBERA™ group lost twice as much weight as the control group and was able to maintain significant weight loss six months after ORBERA™ removal. Additional information about this study and consultation with the investigators is available upon request. In Europe, the current ORBERA™ design, formerly branded as the Bioenterics Intragastric Balloon (BIB), has been on the market outside of the U.S. (OUS) since 2004. More than 280,000 devices have been distributed to over 80 countries. Ten years of OUS clinical product surveillance, more than 200 peer-reviewed publications, and over 80 global randomized controlled trials have demonstrated that ORBERA™ produces clinically meaningful weight loss and quality of life benefits for patients with BMI ≥ 30 with and without co-morbidities. We anticipate similar results post-launch in the United States.	See our response to comment #1 above. As stated in the "Methods" section of the report, evidence on clinical effectiveness was primarily derived from good- and fair-quality RCTs and prospective comparative cohort studies. A detailed description of how we applied quality ratings can also be found in this section.
Steve Chen, MD, Executive Medical Director, US Medical and Scientific Affairs, Takeda Pharmaceuticals International, Chicago, IL		
1	The Contrave prescribing information instructs physicians to discontinue therapy for patients who do not experience a > 5% weight loss after 12 weeks at the maintenance dosage. In the naltrexone/bupropion (N/B) pivotal trials, efficacy results were based on data from all randomized patients with 1 baseline weight measurement and ≥ 1 post-baseline weight measurement, including patients who did not experience significant weight loss and those that discontinued treatment.	Thank you for your comments. Any assessment of overall net benefit must take into account those who did not lose sufficient weight and those who discontinued therapy, so we stand by our evaluation of primary findings from the published RCT reports. Other data, such as the percentage of patients who achieved 5% and 10% total weight loss

	Therefore the efficacy results may not represent current clinical practice.	thresholds, are summarized where reported.
2	Evidence of double-digit weight loss was demonstrated in an integrated analysis of the N/B clinical trials, which evaluated weight loss of early responders defined as ≥ 5% weight loss at week 16 mimicking the Contrave prescribing information. Early responders achieved 11.3% weight loss at 56 weeks, which may more closely represent real world efficacy results. Also at 56 weeks, 85% of patients had ≥ 5% weight loss, 55% had weight loss ≥ 10%, and 30% had ≥ 15% weight loss. Weight loss at week 56 was similar (9.7 kg to 12.4 kg) across four baseline body mass index (BMI) groups: 27-29.9 kg/m^2, 30-34.9 kg/m^2, 35-39.9 kg/m^2, and ≥ 40 kg/m^2.	As noted above, we did not include any data from grey literature, including poster presentations, in the evidence review.
3	On pages ES8 and 62, the draft report assessed N/B as having a "small net benefit" in patients with a BMI from 35-39.9 kg/m^2. In an integrated analysis of the N/B clinical trials where patients on N/B were stratified by baseline BMI groups: 30.0-34.9 kg/m^2, 35.0-39.9 kg/m^2, and ≥40 kg/m^2, weight loss with N/B at week 56 was similar across the 3 obesity classes (N/B range: 6.1% to 7.3%; placebo-corrected range: 4.0% to 5.0%, all $P < 0.001$), as was the categorical weight loss of ≥ 5% weight loss (N/B range: 49% to 54%, odds ratio relative to placebo: 3.5 to 4.3; all $P < 0.001$). Additionally, based on FDA's evaluation of N/B's clinical data, Contrave is indicated for patients with a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥ 1 comorbidity as an adjunct to diet and exercise for chronic weight management. For these reasons, we request that the draft report reflect the efficacy analysis of BMI groups from 27 kg/m^2-35 kg/m^2 consistent with the studies presented above and FDA approved labeling.	See comment #2 above.
4	According to the analytic framework provided in the draft report on pages ES3 and 18, obesity management was evaluated in adolescents and adults classified as overweight or obese with a BMI of ≥ 25 kg/m^2. The population of interest in the report is inconsistent with the population that was studied in the N/B clinical studies, which included adults (18 to 65 years of age) with a BMI 30-45 kg/m^2 for patients with uncomplicated obesity or a BMI 27-45 kg/m^2 for patients with obesity and controlled hypertension and/or dyslipidemia. This study population is reflected in the FDA approved indication. Additionally, the pediatric population was not evaluated and therefore, not recommended for use in this population. We request that the draft report specifically address pharmacotherapy treatment consistent with FDA labeling to provide a balanced picture of the treatment guideline algorithms, which recommend pharmacotherapy treatments prior to considering bariatric surgery and devices.	The analytic framework is intended to convey the target population for the overall evidence review. Limitations based on labeled indications (as well as evidence gaps) are noted separately for each type of intervention. We have clarified the language regarding pediatric patients in our intervention summaries on page ES5.
5	We do not believe that the economic and healthcare benefit of pharmacotherapy, surgery, and devices can be compared	The notion of a treatment continuum was precisely the rationale behind our

	with each other as they provide treatment options for varying patient populations during different stages of the treatment continuum. We recommend incorporating treatment guideline algorithms in evaluating pharmacotherapy treatment options for patients with BMI ≥ 25-35 kg/m^2.	modeling the economic and clinical benefits of certain interventions both alone and in sequence, and contrasting the findings between approaches.
6	In the N/B pivotal trials, secondary markers of cardiovascular and metabolic risk factors besides glycosylated hemoglobin (A1C) were assessed as secondary endpoints. Due to the implications of improving comorbid conditions as a result of weight loss, we recommend providing additional results that summarize the significant effect of N/B on cardiovascular and other metabolic biomarkers (eg, lipid panel, waist circumference).	No changes made to the draft report. As noted in section 4.1, the scope of the review included outcomes related to mortality, weight loss, and improvement/resolution of comorbidities, among others. Changes in laboratory measures were not a focus of the evidence review.
7	Please consider adding additional information related to the benefits of modest weight loss on other comorbidities not included in the report (eg, osteoarthritis, gastroesophageal reflux disease, urinary incontinence, polycystic ovary syndrome/infertility).	No changes made to the draft report. We included results related to the resolution or improvement of comorbidities as available from included studies. Of note, studies that focused exclusively on populations with specific conditions (e.g. Prader Willi syndrome, psoriasis, polycystic ovary syndrome) were excluded unless the condition of interest was a common obesity-related comorbidity such as hypertension, T2DM, sleep apnea, or dyslipidemia. (see section 4.1 for study inclusion/exclusion criteria).
8	While the methodology used to develop the one and ten-year models of clinical and economic outcomes is transparent and reasonable, we suggest that CTAF consider revisions to several critical assumptions upon which these models are based. As previously discussed, assumed use of N/B in the analysis does not reflect the FDA approved label. N/B's label recommends that patients discontinue treatment if they do not achieve ≥ 5% weight loss after 12 weeks at the maintenance dosage. The base case one-year model assumes WAC – 23.1% rebate for N/B's price of 12 months at 100% adherence ($1,645). According to the N/B pivotal trials, 33% of patients exposed to N/B (32 mg/360 mg) discontinued treatment by week 16. Consequently the cost of N/B used in the base case is far greater than it is in actuality, once dropouts are removed from the analysis. Given the N/B label discontinuation guidance, the treatment sequencing sensitivity analysis depicts a greater likelihood of N/B use in clinical practice, and we recommend that this analysis be considered the base case.	The sequential analysis as performed involved discontinuation of N/B for patients not achieving ≥10% weight loss (another endpoint in the RCTs) and switching to RYGB surgery thereafter. Based on this comment, we have now conducted a sensitivity analysis in which the threshold was ≥5%. Results of the two analyses were very similar. Our base case analysis assumed drug discontinuation but only due to adverse events. The pooled rate of discontinuation for this reason across trials was 9.8%.
9	While the prevalence of eligible Medi-Cal adult enrollees is appropriately estimated from NHANES, the assumptions regarding the percentage of patient who would opt for obesity treatment is not robust. According to the US 2013 National	The estimates cited in this comment are cited as "data on file" and are therefore impossible to corroborate. We do agree that there are many reasons why

	Health and Wellness Survey (NHWS), independently conducted by Kantar Health, of individuals with either a BMI of > 30 kg/m^2 or with a BMI > 27 kg/m^2 and an obesity-related comorbidity, only 19.9% spoke to their physician regarding their weight during the previous 12 months. Of these, 5% were prescribed weight loss medications, and 3% and 1% received either a surgical or surgical band procedure, respectively. Consequently, the budget impact estimate for any obesity intervention should be far less than that projected in the CTAF report.	patients do not opt for surgery, including barriers to insurance coverage for those at lower BMI levels. Our intent was to explore the potential budgetary impact if restrictions on access to surgery were removed. Nevertheless, we have added a lower bound of use to the analysis to explore the possible range in budgetary impact.
10	We recommend including the cost of lifetime follow-up care such as nutritional supplements and laboratory testing for individuals receiving bariatric surgery, even if some of these costs are borne by the patient. Severe and costly complications can occur without this continuing treatment and follow-up.	The costs of management post-surgery are included in our estimates as a component of the BMI-linked costs of care but are calculated for 10 years (this was not a lifetime model).
11	Page ES8. N/B is described as "naltrexone (sustained release, 32 mg daily) combined with bupropion (immediate release, 360 mg daily)". Both naltrexone and bupropion in N/B are extended release formulations.	N/B is now described as "naltrexone (extended-release, 32 mg daily) combined with bupropion (extended-release, 360 mg daily)"
12	Page ES8. The total weight loss range from Contrave clinical studies is noted as 5-7.8% with N/B vs 1.2-4.9% with placebo. In four NB pivotal trials, weight loss ranged from 5-9.3% with N/B vs 1.2-5.1% with placebo as specified on page 61.	Total weight loss ranges have been adjusted in the executive summary to correspond with those cited in Section 4.3.3.
13	Page 9. Please revise the wording for the mechanism of action of N/B and reference the primary source (Contrave prescribing information).	The wording of the mechanism of action has been adjusted on page 9 and an additional citation of Contrave's prescribing information has been added.
14	Page 9 and 62 reference the Light Study, a cardiovascular (CV) outcomes trial that terminated early. We recommend referencing Takeda's press release on this topic instead of tertiary sources (ie, Fierce Pharma and Herper). The Herper 2015 resource could not be found in the reference section of the draft report. Another option would be to remove reference to this study until final data have been published as it does not provide additional evidence related to CV safety.	The press release has been added as a reference. We continue to discuss the study given the importance of CV outcomes in this population.
15	Page 60. Please clarify how baseline characteristics (eg, age and gender) were calculated. For the 4 pivotal trial populations combined, the mean age was 46 years and 83% female.	Baseline characteristics, such as age, BMI, and % female, have been adjusted and now describe the weighted average of reported characteristics across the included studies.
Todd Hobbs, MD, North America Chief Medical Officer, Novo Nordisk, Inc., Plainsboro, NJ		
1	Novo Nordisk recommends the exclusion of studies of Victoza® (liraglutide) from review given those studies apply to use of liraglutide up to 1.8mg for treatment of type 2 diabetes rather than treatment of obesity In December of 2014 Saxenda® (liraglutide) was approved by the Food and Drug Administration (FDA) at a dosage of 3mg as	Thank you for your comments. Studies that evaluate liraglutide at doses lower than the indicated 3.0 mg dosage for obesity have been removed from the review.

	a treatment option for adults with either a body mass index (BMI) of 30 or greater or with a BMI of 27 or greater in combination with at least one weight related condition. While Saxenda® and Victoza® are both based on the same active ingredient (liraglutide), Victoza® data is derived from studies where it is used as an adjunct to diet and exercise to improve glycemic control for type 2 diabetes patients and is delivered at lower doses (1.2 or 1.8 mg) than Saxenda® (liraglutide 3.0 mg). In CTAF's analysis of liraglutide, studies comparing lower doses (i.e., less than 3mg) of liraglutide to placebo to gauge effects on blood glucose control, should not be included to assess effects on obesity or weight loss. To accurately assess the efficacy of liraglutide on obesity, Novo Nordisk recommends that CTAF only include the three identified studies, listed in the references below, related to Saxenda® (i.e., liraglutide dosed at 3mg for obesity treatment) in their review and exclude the remaining studies of Victoza® (i.e., liraglutide dosed at 1.2 or 1.8mg for type 2 diabetes).	
2	CTAF should account for the dynamic nature of the obesity treatment landscape and make appropriate accommodations when making any comparisons across treatment modalities given the differences in availability of long-term data on emerging therapeutic options. Within the report, in the Clinical Effectiveness Summary, CTAF notes that given the dynamic nature of obesity the efforts to treat and manage the disease continues to grow as the prevalence also increases. The report does a good job of identifying the challenges associated with the individual types of treatment, including surgical procedures, devices and medications. While all important, Novo Nordisk asks that CTAF not compare each of these differences, as the evidence and patient population for each specific type of treatment will vary. Rather, we ask that CTAF consider comparisons within a treatment path, rather than comparisons across all treatments. Additionally, the data presented to support medications for weight loss needs to consider long-term results related to improvement in co-morbidities, long-term weight trends and health related quality of life. Although this data may not be available today, many of these products are new to the market and will have additional supportive data in the future. This data should be considered and updated to reflect the value of specific medications for this report.	Our organization of the report was intended to reflect the comparison of treatment alternatives within each type of intervention (i.e., surgery, devices, and medications), with the exception of comparisons of surgery to nonsurgical management given the large available evidence base. Also, as noted in the report, we specifically sought long-term data where available. While it is likely that such data may become available in the future for newer interventions, our intent is to summarize the current state of the evidence rather than project what it might appear to be in the future. Future updates to the report will be considered alongside other CTAF topic priorities.
3	Throughout the report, CTAF should make every effort to address all interventions of interest via the same methods of analysis; in instances where this is not possible, the report should clearly explain why specific treatments are omitted. While the report clearly lays out the surgical procedures of interest, the three devices, and four pharmaceutical agents of	We have clarified that the vBloc device and N/B were the other interventions of interest for the model, while the scope of the overall review was broader. However, our justification for limiting the interventions in the model is clearly

	interest, the full complement of therapeutic options are not necessarily addressed in each section of the report. For example, in Section 5, Model of Clinical and Economic Outcomes, when discussing prior published evidence of cost effectiveness of interventions of interest (other than surgical interventions), the report notes only the Maestro vBloc device (and no other devices) and N/B therapy (and no other drug therapies) as "the other treatment options of interest in this review". The exclusion of other device options and the three other FDA-approved pharmaceutical treatments for obesity is inconsistent with the overall focus of the report. We recommend that all stated treatment options of interest be included in each section of CTAF's review. When this is not possible (e.g., newness of product dictates a lack of sufficient evidence of interest), CTAF should clearly outline why specific treatment options were omitted in the specific section for consistency and clarity throughout the entire review.	stated, as vBloc is the only device of interest that is FDA-approved, and N/B had the largest evidence base at an approved dose for obesity management.
Louis J Aronne, MD, FACP¸ Sanford I Weill Professor of Metabolic Research, Weill-Cornell Medical College / Vice Chairman, American Board of Obesity Medicine Rekha B Kumar, MD, MS, Assistant Professor of Medicine, Division of Endocrinology, Diabetes and Metabolism, Weill-Cornell Medical College, Comprehensive Weight Control Center, New York, NY		
1	The title strongly implies that there is a controversy around obesity treatment. However, the word controversy is mentioned only twice in the report, once to describe bariatric surgery, around which there is no controversy – it is effective, and cost effective. At the end of the Executive Summary there is mention of controversy over the significance of BMI values of 25-35 kg/m^2. The age adjusted relative risk of Type II Diabetes Mellitus increases with higher BMI values starting at a BMI of 24 kg/m^2 (Diabetes Care 1994;17:961-969). The fact is, there is no controversy. Obesity is a disease, which should be treated. Given the complexity of body weight regulation, the difficulty has been in finding effective treatments. The major obstacle is a lack of coverage for much of what we do: behavioral obesity treatments to complement medical and surgical therapies, high co-pays and prior authorizations for medications, and various barriers including, in some cases, complete lack of coverage for surgical procedures.	Thank you for your comments. No changes were made to the draft report.
2	The concerns about whether weight loss will be maintained if a patient stops an FDA approved obesity medicine as mentioned in the liraglutide section is inconsistent with our understanding of body weight regulation and management of obesity as a chronic disease. Disease states such as diabetes, hyperlipidemia, or hypertension would recur if medicines for those were stopped. One of the purposes of the AMA's decision to recognize obesity as a disease state is to recognize that it would require long-term management with lifestyle intervention, diet, exercise, as well as long term use of	We have clarified the language to focus on the long-term uncertainties, which revolve around durability of weight loss and safety over longer term follow-up (i.e., greater than two years).

	medicine, devices or surgery to control the hormonal/neurologic abnormalities defining the disease.	
3	Package inserts for the medications recommend not continuing medications past 3-4 months if the patient does not lose 4-5% of body weight. Only those who benefit with medically significant weight loss continue on medication. This increases the benefit and minimizes risk and cost to those who do not respond. This factor does not appear to have been taken into consideration.	We performed a series of sensitivity analysis on key model variables including this parameter. Our original analysis assumed that patients using N/B would switch to RYGB if they did not achieve "success" (10% or more total weight loss). The cost-effectiveness for this sequenced approach was $44,196 per QALY gained vs. standard care. Given that a 5% weight-loss threshold represents a common decision point for whether to continue treatment, we ran an additional analysis using 5% or more total weight loss as the definition of "success". Cost-effectiveness estimates were similar ($41,211 per QALY gained vs. standard care).
4	Given the complexity of the weight-regulating mechanisms, combinations of treatment will be needed and treatments with unique mechanisms of action will be critical. For example, the vBloc Maestro device which you mention has a unique mechanism of action, impacting vagal nerve signaling and affecting afferent weight regulating pathways. The promise of the vBloc Maestro device in combination with a centrally active drug which could produce significantly greater weight loss. This and other minimally invasive therapies that produce consistent results will open up treatment to more patients. Your analysis minimizes the potential benefit, and maximizes the cost and risk of such therapies.	Our analyses focused on treatment effects as estimated from available studies. Analysis of the benefits of treatment combinations as described requires publication of data on the effects of those combinations.
Todd Andrew Kellogg, MD, Surgeon, Mayo Clinic, Rochester, MN		
1	In clinical trials vBloc technology has shown much promise as a treatment option that is safe and effective. Despite exciting short-term results, it is premature to form definitive conclusions regarding the durability and long-term effectiveness of vBloc based on the data currently available, since the device was recently FDA approved and commercial experience and additional data are limited at this point. In summary, current treatment options for obesity are severely limited. vBloc therapy is a technology that has the potential to add an important and novel treatment option for the treatment of this complex and widespread disease.	Thank you for your comments. No changes were made to the draft report.
John B Dixon, MBBS, PhD, FRACGP, FRCP, Head of Clinical Obesity Research, Baker IDI Heart and Diabetes Institute, Melbourne, Australia		
1	The literature review has failed to fully assess the literature. For example, it is hard to exclude the SOS study and have	Thank you for your comments. The SOS study was not included in the meta-

	questionable conclusions about surgery and long-term sustained weight loss. There are many examples of duplicates of single studies getting into your analysis and others missing.	analyses because over two-thirds of the patients received gastroplasty, a procedure no longer performed in the US. We nevertheless summarized the mortality findings of the SOS study on page 29 given its import as a large, long-term cohort study. We also summarized other key clinical outcomes of interest, and the SOS study remains a primary source of long-term data for our economic model. Studies that report various outcomes or therapeutic options are discussed in multiple sub-sections of the report. To understand why some studies might be "missing", please refer to Sections 4.1 and 4.2 for a discussion of our inclusion/exclusion and quality criteria.
2	When dealing with weight loss, use one measure and choose a measure that allows comparisons of different interventions and different cohorts. Actual weight loss favours heavier subjects, percentage excess weight lighter smaller. Percentage weight loss is widely advised as it is balanced for baseline BMI and actually gives us valuable information about health. How could there be two systems for surgery and devices versus lifestyle and medications? Even the leading surgical journals do not permit %EWL as a sole weight loss measure and it has never had an evidence based reason for existing. Please standardize how you express the most basic outcome.	We recognize that there is a controversy in the clinical community surrounding the use of %EWL to measure treatment success. However, given that many studies, particularly those evaluating bariatric surgery, use this metric for evaluating weight loss, we reported these outcomes as stated in the individual studies, but focused on mean change in BMI (such as in our meta-analysis and economic evaluation) or overall weight loss wherever possible.
3	The [CE] analysis is stratified by BMI but health costs are driven by obesity complications not BMI – Diabetes, CV events, physical disability, and OSA. The productivity and community costs need also to be evaluated. The cost of treating diabetes for example may actually be reduced by choosing surgery as suggested in studies of propensity matched groups.	Our estimate of BMI-linked health care costs comes from a population-based study (Ostbye, 2014) that estimates total health care costs by BMI, including management of comorbidities and complications.
4	Table ES1 is very important and really provides the answers to the key questions you are examining. Question – What is the place for any intensive therapies under a BMI of 30? Is there a disconnect between this chart and recommendations from the various US associations? Why is this not a key question? With limited resources why not deliver to those with at least low to moderate evidence?	The intent of Table ES1 is to directly inform all of the voting questions, as it summarizes our judgment of strength of evidence for each intervention and BMI category.
5	This table has another key anomaly that needs addressing. How do you distinguish devices from surgery? LAGB is classified surgery and vBloc a device. How can this be? There are many examples that will challenge these arbitrary divisions as we move forward. It is important to have clarity as, for	We agree that this is something of a grey area, in obesity management as well as many other conditions (e.g., low back pain). We were guided in part by how the interventions were classified in

	example, a beneficial attribute of a device is its removability-reversibility. Strangely, removability (reversibility) by surgeons is seen as a downside, but physicians and patients often see this as a logical and positive attribute. This consideration is important when treating those with class I obesity, younger patients, more elderly patients and those with high risk specific comorbidity. Permanent change, as is clearly the case with sleeve gastrectomy, may not be seen as a positive attribute when we have negligible long term data and an increasing range of medications and devices in the pipeline.	the literature databases, in which LAGB is nearly always referred to as a surgical procedure. Nevertheless, as mentioned previously, our intent was to accurately summarize the state of the evidence on each type of intervention, irrespective of its categorization.