Controversies in Obesity Management

A Technology Assessment

Draft Report

May 26, 2015

Completed by:

Institute for Clinical and Economic Review

©Institute for Clinical and Economic Review, 2015

AUTHORS: Daniel A. Ollendorf, PhD
Chief Review Officer, Institute for Clinical and Economic Review

Karen K. Shore, PhD
Program Director, Institute for Clinical and Economic Review

Chris Cameron, MSc
Senior Decision Scientist, Institute for Clinical and Economic Review

Jed Weissberg, MD, FACP
Senior Fellow, Institute for Clinical and Economic Review

Steven D. Pearson, MD, MSc
President, Institute for Clinical and Economic Review

DATE OF PUBLICATION: May 26, 2015

We would also like to thank Erin Lawler, Anne Loos, Matt Seidner, and Patricia Synnott of ICER for their contributions to this report.

©Institute for Clinical and Economic Review, 2015

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at www.icer-review.org

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – reviews evidence reports and provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care. CTAF is supported by grants from the Blue Shield of California Foundation and the California HealthCare Foundation.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy, all of whom meet strict conflict of interest guidelines, who are convened to evaluate evidence and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at www.ctaf.org

Table of Contents

List of Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
ASMBS	American Society for Metabolic and Bariatric Surgery
BMI	Body Mass Index
BOLD	Bariatric Outcomes Longitudinal Database
BPD	Biliopancreatic Diversion
BPD±DS	Biliopancreatic Diversion with or without Duodenal Switch
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
DEA	Drug Enforcement Agency
DJBL	Duodenal-Jejunal Bypass Liner
DS	Duodenal Switch
EWL	Excess Weight Loss
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
HbA1c	Hemoglobin A1c
HrQoL	Health-Related Quality of Life
HR	Hazard Ratio
IGB	Intragastric Balloon
IWQOL	Impact of Weight on Quality of Life
LAGB	Laparoscopic Adjustable Gastric Banding
LCD	Local Coverage Decision
MAX	Medicaid Analytic eXtract
MBSAQIP	Metabolic Bariatric Surgery Accreditation and Quality Improvement Program
N/B	Naltrexone/Bupropion
NCD	National Coverage Determination
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NS	Not Significant
OR	Odds Ratio
P/T	Phentermine/Topiramate
PHQ-9	Patient Health Questionnaire
PMPM	Per-Member Per-Month
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RR	Risk Ratio
RYGB	Roux-en-Y Gastric Bypass

SF-36	Standard Form – 36
SOS	Swedish Obese Subjects
T2DM	Type 2 Diabetes Mellitus
USPSTF	United States Preventive Services Task Force
vBloc	Vagus Nerve Block
VSG	Vertical Sleeve Gastrectomy

Executive Summary

As the obesity epidemic has spread around the world, a deeper understanding of the drivers of weight gain has emerged. Urbanization; change in diet to more refined foods with high added sugars; differing gut microbiomes, influenced by factors as diverse as breast feeding practices, antibiotic exposure, and dietary fiber; genetics; and our sedentary lifestyle all play a role and have contributed to the redefinition of obesity as a disease, implying the need for medical intervention (American Medical Association, 2013).

A recent estimate found that one-third of American adults and about 17% of adolescents are obese (Ogden, 2014). The health effects of obesity are myriad and include the development of type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease, cancer, high blood pressure, and sleep apnea. Obesity and its sequelae generate an estimated $147 billion in health care costs in the US alone (Finkelstein, 2009).

The complexity involved in managing obesity may affect both patient candidacy for certain treatment options as well as adherence to lifestyle changes necessary to sustain weight loss and improve health outcomes (Magro, 2008). As a result, there is great clinical interest in treatments that may be used for patients at various levels of obesity, as well as in interventions that promote better adherence to lifestyle change.

A panoply of options await the patient seeking or needing to lose weight beyond conventional weight-loss approaches such as general lifestyle counseling, personal dieting, exercise regimens, and commercial weight loss plans. Bariatric surgery remains a mainstay for those with severe or morbid obesity, and it is also being explored in patients with lower levels of obesity (body mass index [BMI] <35 kg/m^2); new devices have emerged or are being tested to suppress appetite and/or reduce food intake through alternative means; and several medications have recently been approved by the FDA specifically for weight loss.

The availability of treatments of differing intensity raises a number of questions, however, including 1) their effects on patients at multiple levels of obesity, 2) their proper place in the treatment continuum for any given group of patients, and 3) their performance and durability of treatment effects over the long term.

The purpose of this report for CTAF, therefore, is to examine the comparative clinical effectiveness and comparative value of surgical-, device-, and medication-based treatments in relation to conventional weight-loss management as well as across intervention types. Special attention is also paid to studies conducted in individuals at lower levels of BMI (i.e., 25-35 kg/m^2), a key area of uncertainty and controversy.

Scope of the Assessment

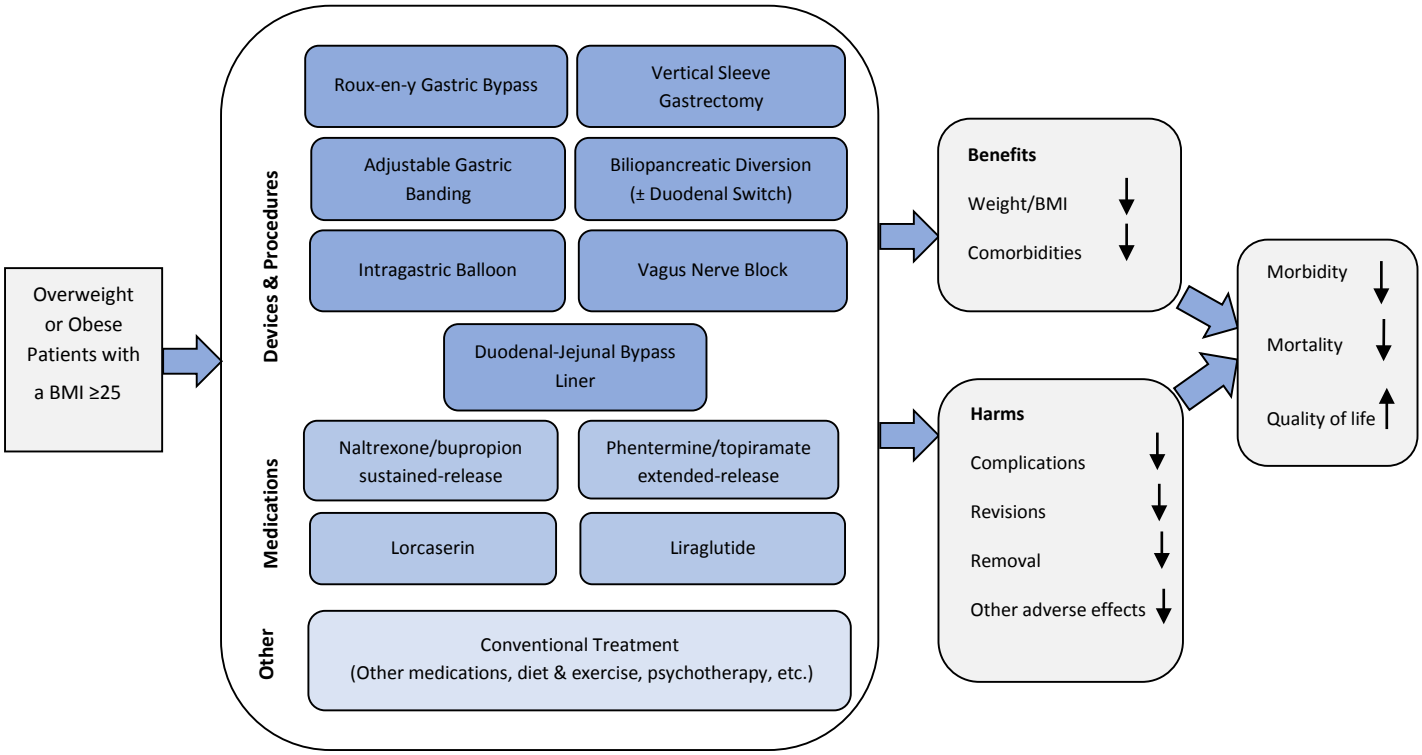
Our primary goal for this assessment was to compare the evidence on clinical benefits and harms for surgical procedures, devices, and medications of interest in this review to that of conventional weight-loss management (i.e., combinations of diet, exercise, and/or behavioral and lifestyle interventions). However, we also included studies that actively compared different types of interventions, both across (e.g., device vs. surgery) and within (e.g., gastric bypass vs. gastric banding) categories where available.

Evidence on clinical benefit and harms was primarily derived from good- and fair-quality randomized controlled trials (RCTs) and prospective comparative cohort studies. Retrospective comparative cohort studies were summarized where feasible – particularly for harms data, given the large sample sizes available in these types of cohorts. Finally, case series of >50 patients were considered only for evidence on harms and long-term benefit. Surgical series were limited to those with two or more years of follow-up given the expected maturity of this evidence base. However, given that follow-up for emerging devices and drugs is not yet likely to be adequate to impose such a threshold, and/or is limited by the intervention approach itself (e.g., temporary balloon insertion), we did not impose a strict follow-up limit on these case series.

Analytic Framework

The analytic framework for this evaluation is depicted in Figure ES1 on the next page. Because there were expected limitations on the impact of obesity interventions on long-term measures of morbidity, mortality, and health-related quality of life (HRQoL), a series of conceptual links was required to tie shorter-term impact on measures of body weight and resolution of or improvement in key comorbidities to longer-term outcomes.

Figure ES1. Analytic Framework for Evaluation of Obesity-related Treatments



Interventions

For assessment of surgery, studies were limited to those that involve the four bariatric procedures shown in Figure ES1 and commonly used in the US: Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), vertical sleeve gastrectomy (VSG), and biliopancreatic diversion with or without duodenal switch (BPD±DS). We also considered the evidence for three newer types of devices and four medications listed below:

Devices: temporary intragastric balloon systems (IGB) (e.g., Silimed®, ReShape®), duodenal-jejunal bypass liner (DJBL) (EndoBarrier®), and vagus nerve block devices (e.g., Maestro® system).

Medications: liraglutide (Saxenda®), lorcaserin (BELVIQ®), naltrexone/bupropion sustained-release (N/B) (Contrave®), and phentermine/topiramate extended-release (P/T) (Qsymia®)

We focused on devices and medications that are approved by the Food and Drug Administration (FDA) for weight loss or are imminently expecting FDA approval. Note that interventions differ in terms of their approved indications, these differences are noted where relevant in the full report.

Comparative Effectiveness and Safety

Evidence on comparative clinical effectiveness and safety is described separately for bariatric surgery, devices, and medications in this report. Because evidence in patients with BMI <35 was deemed to be of particular interest, findings for this subpopulation are highlighted separately for each intervention in the full report. Of note, although each of the included medications is intended for patients with a BMI ≥30 (or >27 with comorbidities), the mean baseline BMI of patients across studies was approximately 36. As such, evidence of the effectiveness and safety of the medications of interest in patients with lower BMI levels is extremely limited.

Table ES1 below summarizes the level of certainty in the evidence according to BMI category, as well as by the presence of T2DM, the comorbidity most commonly studied for BMI levels <30 and 30-34.9. Because uncertainties remain with long-term outcomes and durability of clinical benefit across all interventions, we did not consider the evidence to provide high levels of certainty for *any* intervention. Across interventions, the evidence is strongest for surgery, as well as for all interventions in patients with a BMI ≥35. A detailed summary of the evidence for each intervention type is described in section 4 of the full report.

Table ES1: Strength of Evidence by BMI Category

BMI	<30		30-34.99		35-39.99	≥40
T2DM	Yes	No	Yes	No	---	---
Bariatric Surgery						
BPD						
LAGB						
RYGB						
VSG						
Devices						
IGB						
DJBL						
vBloc						
Drugs						
Liraglutide						
Lorcaserin						
N/B						
P/T						

Key
No evidence
Low certainty
Moderate certainty
High certainty

Clinical Effectiveness

Bariatric Surgery

Across a range of procedures, study designs, and duration of follow-up, bariatric surgery results in greater sustained weight loss (on average, 7-8 BMI points, or 30-40% of total body weight) and resolution of comorbidities (primarily T2DM) than nonsurgical management. These results are limited by a lack of good-quality long-term data on durability of benefit. There is also a lack of both short- and long-term data demonstrating effectiveness for any bariatric surgery procedure in both children and adolescents. There is little to distinguish performance of individual bariatric procedures, as LAGB use has declined substantially, BPD±DS is technically complex and performed only at certain centers, and the performance of RYGB and VSG is similar.

Evidence on the differential effectiveness and safety of bariatric surgery procedures according to patient characteristics such as age, gender, race/ethnicity, BMI, or psychosocial factors is largely inconclusive. Nevertheless, there is evidence, albeit limited, that surgeon experience, high procedure volume, multidisciplinary care, adherence to pre- and post-operative follow-up, and post-procedure support may positively influence outcomes.

For patients with a BMI of 35 and above with or without clinical comorbidities, we judge there to be moderate certainty of a substantial net health benefit of bariatric surgery compared to nonsurgical management; certainty remains moderate because of a lack of long-term data on durability of benefit. For individuals with a BMI 30-34.9, we judge there to be moderate certainty of a small-to-moderate net benefit of bariatric surgery compared to nonsurgical management only among patients with T2DM who receive RYGB or LAGB procedures. The evidence base provides low certainty for all other procedures and for any surgery in this BMI range in patients with comorbidities other than T2DM. Our judgement of the net benefit of bariatric surgery relative to nonsurgical management in pediatric populations is ”insufficient”, as we found only one good-quality RCT of 50 patients that evaluated outcomes in this population. Finally, we found no evidence of the effectiveness of bariatric surgery in patients with a BMI <30.

Intragastric Balloons (IGB)

Temporary IGB insertion was associated with statistically-significant improvements in measures of weight change at a median of one year of follow-up relative to conventional approaches (e.g., diet, exercise, behavioral modification). Benefits were modest, however – higher-quality studies showed incremental BMI changes and percentage weight loss of 1-3 points and 4-8%, respectively – and also tended to worsen after balloon removal (typically after six months). There was great variability in study design, duration of follow-up (particularly after balloon removal), and treatment approach (i.e., single vs. multiple balloon insertions).

Evidence comparing IGB to bariatric surgery was mixed; several studies showed greater weight loss with IGB vs. LAGB, but differences diminished with greater duration of follow-up. Data are limited on all other outcomes, including resolution of comorbidities and QoL, and in populations with a BMI less than 35. Although there is insufficient evidence on the long-term durability of treatment effect or safety of IGB therapy following balloon removal, weight regain appears to be common, and major treatment-related complications are rare.

We judge there to be low certainty of a comparable net benefit for temporary IGB insertion relative to either lifestyle intervention or bariatric surgery in patients with a BMI ≥35. In comparison to lifestyle interventions, IGB therapy appeared to provide modest reductions in weight across studies, but data on weight change were mixed after balloon removal, there was variability in balloon duration and number of placements, and there is the potential for harm. Evidence of benefit was truly mixed in available comparisons of IGB to bariatric surgery. Evidence on the benefit of the balloon in patients with a BMI <35 or its impact on any other outcome is insufficient to draw any firm conclusions.

Duodenal-Jejunal Bypass Liner *(EndoBarrier®)*

We identified one good- and one fair-quality RCT, both of which were conducted in patients with BMI levels of 35 or greater, that compared the DJBL to conventional weight-loss treatment. Neither study found statistically significant differences in reduction of mean BMI between control and DJBL patients. Patients in both studies reduced or discontinued anti-diabetic medications; however, data on comorbidities were not reported for control patients in one study, and statistical testing for differences was not conducted in the other. We found no studies that had a patient population with mean BMI <35 or that reported on other outcomes of interest. Complications of the DJBL included device or anchor migration, epigastric pain, and sleeve obstruction; 2.9-20.5% of patients had the device removed prematurely across studies. Finally, enrollment in a large clinical trial of DJBL is currently stopped pending investigation of a higher-than-expected rate of bacterial infection.

This preliminary evidence suggests that there is low certainty that the DJBL has a comparable net health benefit or possibly even a negative net health benefit for weight loss and comorbidity resolution relative to lifestyle interventions in patients with a BMI ≥35, and no evidence at all in patients at lower BMI levels. Given this level of certainty, and both published and manufacturer-reported data on potentially serious harms, we judge the current evidence to be insufficient to draw firm conclusions on the DJBL's effects.

Vagus Nerve Block *(Maestro®)*

We identified two RCTs that examined the vBloc device. After 12 months follow-up in each study, vBloc patients lost 17-24.4% of excess body weight versus 15.9-16.0% excess weight loss (EWL) in

control patients. The included studies did not report outcomes related to resolution or improvement in comorbidities. In both studies, 5.4% of patients had the device removed before study end; 3.4-4.4% of patients experienced serious complications related to the device, implantation, or revision.

We judge there to be low certainty of either a small or comparable net benefit for the vBloc device compared to a sham device in patients with a BMI ≥40, and the impact of the vBloc on comorbidities has not yet been determined. Given these results, and a not-inconsequential rate of device removal, we judge the evidence to be insufficient to draw firm conclusions on the benefits of the vBloc system in these patients. We found no evidence of the vBloc's effects in patients with BMI levels <40.

Medications

A number of medications have recently been approved for the treatment of obesity or overweight, and these are described below. All are indicated for use in patients with a BMI ≥30 or in those with a BMI ≥27 who have at least one weight-related comorbidity.

Liraglutide (Saxenda®)

The two studies with labeled dosing for weight loss (3 mg) found that patients lost 6-8% of total body weight after one year of follow-up and were more likely to have normal glucose tolerance relative to those in the placebo group. Changes in quality of life (QoL) were inconsistent across studies. The most commonly reported adverse effects (AEs) were gastrointestinal disorders including nausea, vomiting, diarrhea, and constipation. Overall AE rates ranged from 21-95.7% across studies, and discontinuation due to AEs ranged from 0-15.0%.

We judge there to be low certainty that dosing of liraglutide for weight loss provides a small net benefit vs. lifestyle interventions in patients with a BMI ≥30, due to modest levels of incremental weight loss and comorbidity resolution. Certainty was judged to be low because only two of the 11 available RCTs evaluated liraglutide at currently-labeled dosing for weight loss. It is also uncertain whether the benefits conferred from liraglutide can be sustained once treatment is discontinued or whether it can be safely taken for durations longer than one year. We found no evidence of liraglutide's benefits in patients with BMI levels <30.

Lorcaserin (BELVIQ®)

In the three good-quality RCTs, reductions in total body weight were modest, ranging from 4.5-5.8% among lorcaserin recipients, compared to a 1.5-2.8% mean decrease among those taking the placebo ($p<0.001$ for lorcaserin vs. placebo in all studies). A single study reported outcomes related to comorbidity status and found 50.4% of lorcaserin patients versus 26.3% of placebo patients

achieved a hemoglobin A1c (HbA1c) <7% (p>0.001) (O'Neil, 2012). Discontinuation of lorcaserin from drug-related AEs occurred in 4.3-8.6% of patients across studies, and approximately 80% of study participants experienced any AE.

We judge there to be moderate certainty of a small net benefit of lorcaserin (10 mg, administered once or twice daily) over lifestyle modification for weight loss in patients with BMI levels between 35-39.9. There is moderate certainty because while three good quality studies reported consistent weight-loss results, two studies excluded patients with common obesity-related comorbidities. We found no evidence of lorcaserin's benefits in populations with BMI levels ≤35 or ≥40.

Naltrexone/Bupropion (Contrave®)

Across five available RCTs, participants who received standard doses of naltrexone (sustained release, 32 mg daily) combined with bupropion (immediate release, 360 mg daily) lost 5-7.8% of total body weight after a median duration of follow-up of 56 weeks; patients who received a placebo lost 1.2-4.9% of total body weight. A single RCT reported outcomes related to improvement of comorbidities and found that 44.1% of patients taking N/B achieved a target HbA1c <7% compared to 26.3% of placebo patients (Hollander, 2013). Discontinuation of N/B from AEs occurred in 4.3-29.3% of patients receiving standard-dose N/B across studies, and 60.0-90.4% of patients experienced any AE.

We judge there to be moderate certainty of a small net benefit associated with N/B over placebo, naltrexone monotherapy, or bupropion monotherapy with lifestyle intervention in patients with a BMI between 35 and 39.9. There is moderate certainty of benefit because although five good- or fair-quality studies showed consistent weight loss relative to comparator treatment, benefits were modest and more than half the patients in any individual study experienced a treatment-related AE. We also judge the evidence to be of low certainty for a small net benefit in patients with BMI 30-34.9 and T2DM based on the results of a single RCT in this population. Evidence was judged to be insufficient for all other BMI levels.

Phentermine/Topiramate (Qsymia®)

We identified a total of eight good- or fair-quality reports from five RCTs that compared phentermine/topiramate (P/T) extended release combination therapy to a placebo or to phentermine or topiramate monotherapy, all but one of which were conducted in patients with BMI levels between 35 and 39.9. In these trials, patients receiving the initial recommended dose combination (7.5/46 mg) lost 7.8-8.5% of total body weight (vs. 1-2% for placebo), while the range for those receiving the higher dose (15/92 mg) was 9.2-10.9%. Patients who received any dose of P/T experienced greater improvement in obesity-related comorbidities such as T2DM, hypertension, and sleep apnea. We found no studies that had a patient population with mean BMI

<35. Overall, 91-95% of patients experienced one or more AEs and 1.3-16.0% discontinued P/T due to AEs.

We judge there to be moderate certainty of a small net benefit for P/T in improving weight loss relative to lifestyle modification and/or monotherapy of phentermine or topiramate in patients with BMI levels 35-39.9, and a low certainty of the same benefit in those with BMI ≥40. As with the other medications, certainty was low or moderate because of the modest levels of weight loss and comorbidity resolution observed, balanced against high rates of discontinuation due to AEs with this scheduled medication. We found no evidence on benefits in patients with BMI levels <35.

Clinical Effectiveness Summary

Our review of the evidence suggests that obesity treatment is a dynamic and changing clinical area, and that efforts to innovate have grown along with the prevalence of the clinical problem itself. That said, there are distinct differences and challenges with the level and types of evidence available for surgical procedures, devices, and medications.

The evidence base for surgery is the most mature, and comparative data on procedures has accelerated in recent years (two-thirds of the publications in our sample were published after 2011). For morbidly obese (BMI ≥40) and severely obese (BMI 35-39.9) patients with comorbidities, bariatric surgery consistently outperforms nonsurgical treatment approaches in terms of sustained weight loss (7-8 BMI points, or 30-40% of total body weight) and resolution of comorbidities. There are clearly tradeoffs to consider, as each individual procedure confers its own level of complication and reoperation risk. However, the choice of procedure has essentially narrowed to gastric bypass or sleeve gastrectomy; current trends suggest that gastric banding has fallen out of favor due to lower effectiveness, and biliopancreatic diversion is a technically-demanding and much less-frequently performed operation. Nevertheless, our conclusions on the benefits of any bariatric procedure are challenged somewhat by a general lack of high-quality long-term data on effectiveness, safety, weight regain, and return of comorbidities.

In patients at lower levels of BMI (30-34.9), evidence for bariatric surgery is prominent among patients with T2DM and relatively consistently shows substantially greater levels of diabetes improvement or resolution vs. intensive lifestyle and medical management. Lack of long-term data is also a challenge with these studies, however, and comparative data for bariatric surgery in patients with lower BMI levels and other types of comorbidities are lacking.

Regardless of surgical approach or outcome of interest, there are data to suggest that there are core bariatric program components associated with success. Unfortunately, the best data are on elements (e.g., surgeon volume, learning curve) that are important for *any* surgical procedure, and

evidence on other components (e.g., care team members, accreditation, psychological testing, pre- and/or post-operative support) are mixed at best or lacking.

By contrast, information for devices is truly emerging. For one, the only FDA-approved device among the three types of interest in our review is the Maestro vBloc system; even with this approved device, benefits are modest (mean difference of 8.5% of body weight lost vs. sham device) in one RCT, no benefit was observed in another, and device removal for AEs or other reasons is not uncommon. More comparative data are available on temporary intragastric balloon insertion, but benefits are again modest (4-8% total weight loss), there is a high rate of early removal due primarily to persistent nausea and vomiting, and there are very little reliable data on trends in body weight after balloon removal. Limited available data on the EndoBarrier DJBL show no material benefit over control therapy, and the current registrational clinical trial has been suspended due to safety concerns.

Finally, all four of the newer weight-loss medications have been FDA-approved, but benefits are again relatively modest in comparison to conventional weight-loss management. Across all four medications, total weight loss ranged from 3-7% in comparison to placebo or active comparator therapy. In addition, there are limited data on resolution or improvement in comorbidities, lack of information on long-term weight trends, high rates of discontinuation in many studies, and not-inconsequential concerns about potential to harm (two of the four are scheduled substances). Of interest to this review, none of the drugs of focus provide any comparative evidence in overweight but non-obese subjects (i.e., BMI 25-30), despite the fact that the labeling for all four allows for use in such patients.

Economic Outcomes

Published evidence accumulated to date on care value (see Section 5 of the report for details) suggests that bariatric surgery meets commonly-accepted thresholds for cost-effectiveness in comparison to standard care across multiple BMI categories, time horizons, and procedure types. By contrast, there are no currently published estimates of cost-effectiveness for newly-approved devices and drugs such as vBloc and Contrave®.

To better inform the comparisons of interest in our review, we developed a simulation model to compare the care value of four bariatric surgery procedures, the Maestro® vBloc system, and N/B sustained-release (Contrave®) to conventional weight-loss management for all obese individuals (BMI ≥30), as well as for subgroups defined by BMI range (i.e., 30-34.9, 35-39.9, and ≥40). Over the course of one year, across all levels of BMI and procedure type, we found that all interventions improved BMI levels but were subject to varying levels of complications and AEs, as well as increased overall costs. Over a 10-year timeframe, each intervention also resulted in improved quality-adjusted survival due primarily to the beneficial effects of lower weight on QoL. The more

prominent weight loss from surgery also lowered obesity-related costs, offsetting the initial costs of surgery by as much as 30% over 10 years.

Cost-effectiveness estimates for bariatric surgery over 10 years ranged from approximately $24,000 to $63,000 per quality-adjusted life year (QALY) gained vs. conventional treatment, which is within commonly-accepted thresholds for cost-effectiveness (i.e., $50,000-$100,000 per QALY gained). These findings were robust to a range of sensitivity analyses, including elimination of mortality benefit for bariatric surgery and complete weight regain five years after surgery. Importantly, while the most favorable results were seen in patients with BMI ≥40 due to greater weight loss (and corresponding gains in QoL), surgery produces cost-effectiveness ratios within the commonly-accepted range among those with a BMI level of current policy interest (30-34.9), with findings ranging from $43,000 - $63,000 per QALY gained vs. conventional treatment.

In contrast, the much more modest weight loss achieved with the vBloc device and N/B pharmacotherapy, coupled with their high implantation and ongoing therapy costs, respectively, resulted in much higher cost-effectiveness ratios (>$100,000 per QALY vs. conventional treatment). Results were more favorable when these treatment options were considered "in sequence" with bariatric surgery for those failing initial treatment, in particular for a "drug first" regimen in which those with successful weight loss at one year continued to receive medication while patients requiring surgery were able to receive surgery after an initial weight loss.

Given the emerging nature of the evidence on devices and the modest benefits afforded by newer medications, we opted to focus our health-system value analysis on the use of bariatric surgery in patients with a BMI of 30-34.9. Under the assumption that 25% of adults currently enrolled in Medi-Cal would opt for vertical sleeve gastrectomy (the least expensive procedure in widespread use) over conventional weight-loss management, the one-year budgetary impact is substantial – $66, or a 12% increase over the current total per-member per-month (PMPM) Medi-Cal expenditure rate of $552. When availability is restricted to the subset of these patients who have diabetes, however, the budgetary impact declines to approximately $7 PMPM, or a 1.3% increase.

While findings from both our evidence review and assessment of comparative value are intriguing, gaps in available evidence continue to pose challenges in understanding the appropriate sequence of treatments and relevant candidates for each option along the treatment continuum. There is a need for rigorous long-term and comparative study to better understand the durability of weight loss and comorbidity resolution, as well as patterns of harm over longer durations of follow-up.

Introduction

A recent estimate found that one-third of American adults and about 17% of adolescents are obese (Ogden, 2014). The health effects of obesity are myriad and include the development of type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease, cancer, high blood pressure, and sleep apnea. Obesity and its sequelae generate an estimated $147 billion in health care costs in the US alone (Finkelstein, 2009).

The complexity involved in managing obesity may affect both patient candidacy for certain treatment options as well as adherence to lifestyle changes necessary to sustain weight loss and improve health outcomes (Magro, 2008). As a result, there is great clinical interest in treatments that may be used for patients at various levels of obesity, as well as in interventions that promote better adherence to lifestyle change.

A panoply of options await the patient seeking or needing to lose weight beyond conventional weight-loss approaches such as general lifestyle counseling, personal dieting, exercise regimens, and commercial weight loss plans. Bariatric surgery remains a mainstay for those with severe or morbid obesity, and it is also being explored in patients with lower levels of obesity (body mass index [BMI] <35 kg/m^2); new devices have emerged or are being tested to suppress appetite and/or reduce food intake through alternative means; and several medications have recently been approved by the FDA specifically for weight loss.

The availability of treatments of differing intensity raises a number of questions, however, including 1) their effects on patients at multiple levels of obesity, 2) their proper place in the treatment continuum for any given group of patients, and 3) their performance and durability of treatment effects over the long term.

The purpose of this report for CTAF, therefore, is to examine the comparative clinical effectiveness and comparative value of surgical-, device-, and medication-based treatments in relation to conventional weight-loss management as well as across intervention types. Special attention is also paid to studies conducted in individuals at lower levels of BMI (i.e., 25-35 kg/m^2), a key area of uncertainty and controversy.

1. Background

1.1 Background

More than one-third of adults and about 17% of adolescents are obese (Ogden, 2014). The health effects of obesity are myriad and include the development of type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease, high blood pressure, and sleep apnea. Obesity and its sequelae generate an estimated $147 billion in health care costs in the US alone (Finkelstein, 2009).

Historically, options for treating obesity have been limited to lifestyle modifications such as dietary changes and exercise, as well as the use of weight-loss medications and dietary supplements, all of which have struggled to show evidence of persistent and long-term weight reduction. In addition, earlier-generation medications were often found to pose significant health risks of their own (National Institutes of Health, 2013).

More recently, additional treatment options have become available for significant obesity. Most prominently, use of surgical interventions has become more widespread. The term "bariatric surgery" refers to a collective group of procedures that involve modifications to the digestive system that promote weight loss; procedures currently performed in US settings include gastric bypass, gastric banding, sleeve gastrectomy, and biliopancreatic diversion (with or without duodenal switch) (National Institutes of Health, 2009). Most patients are able to undergo these procedures via laparoscopy. The choice of procedure depends primarily on the severity of obesity, the presence of comorbid conditions, the experience of the surgeon, and the patient's individual preferences or other contraindications (Colquitt, 2014).

In certain settings and populations, bariatric surgical procedures have resulted in substantial reductions in body weight and remission of some obesity-related comorbidities (e.g., hypertension, diabetes). Long-term observational studies also suggest that bariatric surgery may reduce the risk of newly developing these comorbidities (Booth, 2014; Sjöström, 2012), an important consideration in adolescents or adults without longstanding obesity. Early use of the procedures focused on individuals meeting criteria for severe or morbid obesity (BMI ≥35.0 kg/m^2) who had at least one obesity-related condition. Subsequent studies have been conducted in individuals at lower levels of BMI, which has led to regulatory approval specific to this population: in 2011, the Food and Drug Administration (FDA) approved the use of a laparoscopic adjustable gastric banding (LAGB) device in patients with lower levels of obesity (BMI 30.0-34.9) and at least one obesity-linked condition (U.S. FDA, 2011).

Clinical interest remains high in expanding the use of bariatric surgery to a broader set of individuals. Questions remain, however, regarding the performance of these procedures in these

patients versus those with higher levels of obesity as well as the health-system impact given the higher prevalence of moderate obesity versus severe/morbid obesity. An additional and considerable challenge to the potential expansion of bariatric surgery is a lack of long-term data on the safety and effectiveness of these procedures. A recent systematic review attempted to quantify the number of studies with sufficient long-term follow-up and found that only 29 (2.6%) of 1,136 long-term studies maintained at least 80% of the original sample after two or more years (Puzziferri, 2014). In addition, even those studies with sufficient sample retention were often missing data on weight changes and comorbidity remission. Long-term follow-up is perhaps even more critical with bariatric surgery than in other clinical areas, as weight regain is not an uncommon phenomenon (Magro, 2008).

There are also specific risks associated with bariatric procedures, which may include bowel obstruction, development of gallstones or hernias, stomach perforation and ulcer, "dumping syndrome" (diarrhea and other related symptoms caused by rapid movement of undigested food to the small bowel), and in some cases, death (Mayo Clinic, 2014). Additional surgeries may be required as part of a multi-phase procedure (as with biliopancreatic diversion), to implement an entirely new treatment modality, remedy a complication, or reverse the procedure altogether if complications are life-threatening (Brethauer, 2014). Surgical revisions comprise about 6% of all weight loss surgeries performed annually in the US (American Society for Metabolic and Bariatric Surgery (ASMBS), 2014).

Because of the complexities, risks, and uncertainties that remain with even well-accepted bariatric surgical procedures, there is continued interest in the development of less-invasive approaches to weight loss. New medications have recently been approved specifically for weight loss, including serotonin receptor agonists for appetite suppression, anti-diabetic medications with known weight-loss effects, and fixed-dose combinations such as phentermine/topiramate (P/T) and naltrexone/bupropion (N/B) that have been studied and/or approved individually for weight loss (The Medical Letter, 2015). Several devices are also under active study, including a recently-approved vagus nerve-blocking system, a plastic barrier to reduce food absorption, and temporary intragastric balloons (IGB) to reduce food intake and promote satiety (US FDA, 2015).

Because the role of each type of intervention across multiple levels of obesity remains uncertain, this review focuses on the evidence for comparative clinical effectiveness and comparative value for each intervention of interest in relation to conventional weight-loss management as well as available head-to-head studies across intervention types. Interventions of interest for this review are described in further detail in the following section.

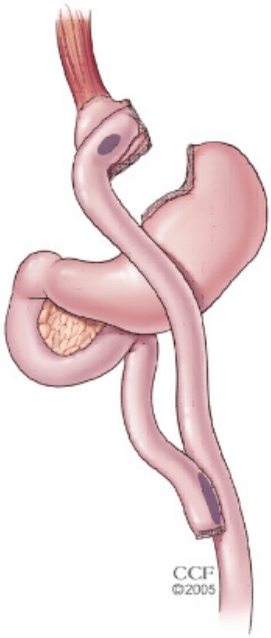
1.2 Treatment Strategies of Interest

Bariatric Surgery

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) is the most commonly performed bariatric procedure worldwide (ASMBS, 2015). RYGB can be performed laparoscopically, robotically, or through a traditional open approach and typically lasts one-and-a-half to four hours.

Figure 1: Roux-en-Y Gastric Bypass



Source: http://asmbs.org/patients/bariatric-surgery-procedures

During the procedure, a surgeon separates the upper and lower portions of the stomach by creating a small pouch in the top of the stomach. The pouch is approximately two tablespoons in volume, and it is intended to restrict food intake and promote satiety after small amounts of food are consumed (University of Illinois Bariatric Surgery Program, 2015).

The remaining portion of the stomach is bypassed by dividing the small intestine into two limbs: the Roux limb and the biliopancreatic limb. The Roux limb, which is also referred to as the jejunum, is the middle section of the small intestine. This limb is connected to the gastric pouch so that food bypasses both the lower portion of the stomach and the beginning portion of the small intestine. The biliopancreatic limb, which contains the beginning part of the small intestine, is reconnected below the Roux limb so that digestive juices from the remnant stomach may flow to the remaining intestine. The intersection of the biliopancreatic and Roux limbs forms the shape of a "Y," giving this procedure its name. The bypass causes malabsorption, in which patients absorb fewer calories and nutrients from food.

After RYGB, patients remain in the hospital for one or two nights and recover within approximately one month. Possible complications include bleeding, pouch ulcers, dehydration, leakages, internal hernias, blockages, blood clots, and infection. "Dumping syndrome" can occur when food and digestive juices move to the small intestine at an abnormally fast pace. Patients are also required to take nutritional supplements for the remainder of their lives and monitor their intake of carbohydrates to avoid gastric discomfort, vomiting, and diarrhea.

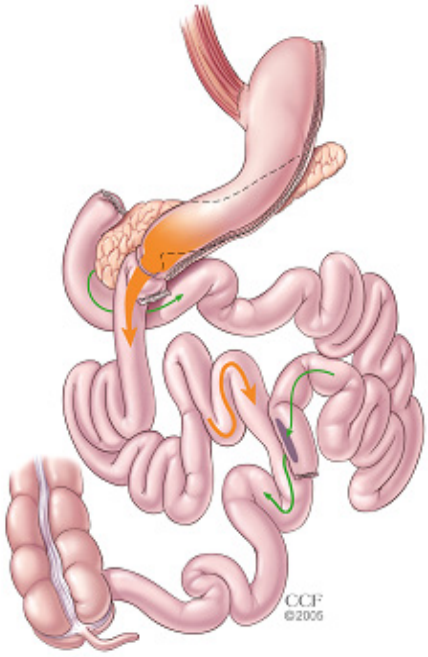
Biliopancreatic Diversion with or without a Duodenal Switch (BPD±DS)

Biliopancreatic diversion is commonly performed on individuals with a BMI of 50 kg/m^2 or greater (Mayo Clinic, 2015). BPD first involves the removal of about 70% of the stomach in order to reduce acid production. The remaining portion of the stomach is larger than the pouch formed by RYGB, which allows the patient to ingest more food before feeling satiated (Kaleida Health, 2015).

The small intestine is then divided and one end is attached to the new stomach pouch, creating an "alimentary limb" through which food travels with limited calorie and nutrient absorption. Digestive enzymes travel through a biliopancreatic limb that is connected near the end of the small intestine, meeting up with ingested food and forming a common limb. While the resulting anatomy of this procedure is similar to that of RYGB, the intestine length from stomach to colon is much shorter in BPD (ASMBS, 2015).

The duodenal switch (DS) is a modification of the biliopancreatic diversion. Instead of removing the lower half of the stomach (as with the BPD), the DS cuts the stomach vertically and leaves a tube of stomach that empties into a very short (2-4 cm) segment of duodenum (ASMBS, 2015). Whereas the BPD involves forming a connection between the stomach and the intestine, the DS preserves the duodenum, attaching this upper portion of the small intestine to the lower portion of the small intestine.

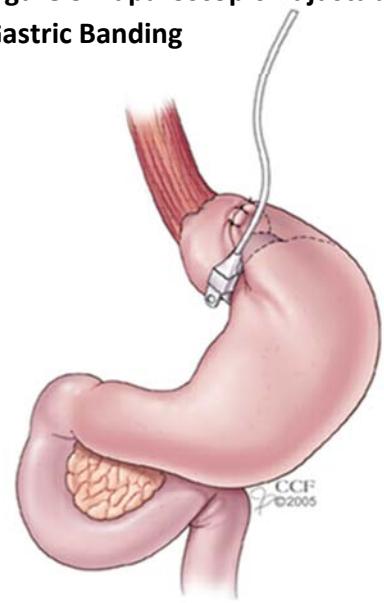
Figure 2: Biliopancreatic Diversion/Duodenal Switch



Source: http://asmbs.org/patients/bariatric-surgery-procedures

Patients typically remain in the hospital for four to seven nights after BPD and take three to four weeks to recover. As with RYGB, BPD±DS is a malabsorptive procedure that requires patients to remain on vitamin and mineral supplements for the remainder of their lives. Possible complications may include kidney stones, ulcers, internal bleeding, infection, blood clots, hernias, dumping syndrome, and death. Additionally, patients are prone to diarrhea and foul smelling gas, with an average of three to four loose bowel movements a day.

Figure 3: Laparoscopic Adjustable Gastric Banding



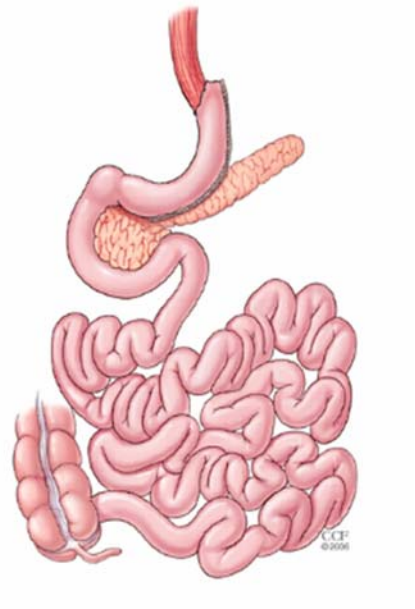
Source: http://asmbs.org/patients/bariatric-surgery-procedures

Laparoscopic Adjustable Gastric Banding (LAGB)

Adjustable gastric banding is a purely restrictive procedure that induces weight loss by restricting food intake. During the procedure, a band containing an inflatable balloon is fixed around the upper part of the stomach. This creates a small stomach pouch above the band with a narrow opening into to the rest of the stomach (Mayo Clinic, 2015). The band can be adjusted by injecting or removing fluid from the balloon through a port under the skin of the abdomen. After surgery, some patients spend a night at the hospital while others recover at home. After one week, patients can return to work, provided it is not too physically taxing, and are usually fully recovered within one to two weeks.

Unlike other bariatric procedures, LAGB is a reversible procedure with a lower risk of nutritional deficiencies and lower mortality. However, optimal results require frequent follow-up visits for band adjustments. Complications can include hemorrhage, port infection, band infection, obstruction, nausea, vomiting, band erosion into the stomach, and esophageal dilation.

Figure 4: Vertical Sleeve Gastrectomy



Source: http://asmbs.org/patients/bariatric-surgery-procedures

Vertical Sleeve Gastrectomy (VSG)

Vertical Sleeve Gastrectomy (VSG) can be performed as part of a two-staged approach to surgical weight loss or as a stand-alone procedure. Patients who have a very high BMI, are at high risk for surgical complications from longer procedures, have an excessively large liver, or have extensive scar tissue are considered possible candidates for sleeve gastrectomy (Cleveland Clinic, 2015). Patients sometimes return to the hospital to undergo RYGB as a second stage procedure after VSG.

Similar to BPD±DS, 60-75% of the stomach is removed during VSG, leaving a narrow gastric "tube" or "sleeve" (Cleveland Clinic, 2015). This small remaining "tube" cannot hold as much food and produces less of the appetite-regulating hormone ghrelin, lessening a patient's desire to eat.

If conducted laparoscopically, sleeve gastrectomy requires an overnight hospital stay, and recovery time is approximately one to two weeks. VSG is not a purely malabsorptive procedure, so there is no requirement for lifetime nutritional supplementation. Potential complications include bleeding, infection, injury to other organs, and leakage from the staple line that divides the stomach (Cleveland Clinic, 2015).

Devices

EnteroMedics vBloc®/Maestro System®

The newly FDA-approved Maestro system is a subcutaneous implant that generates an intermittent electrical pulse that blocks the vagus nerve, the primary nerve regulating the digestive system, in order to reduce feelings of hunger and promote earlier feelings of satiety. Pulse frequency and intensity can be modified externally by the physician (EnteroMedics, 2015a). The device has been approved for adults with a BMI of 40 to 45 kg/m^2 or a BMI of 35 and greater accompanied by at least one other obesity-related comorbidity. Adverse events reported during a recent clinical study of the Maestro system included complications related to intra-abdominal surgery, nausea and vomiting, implant site pain, heartburn, difficulty swallowing, and intestinal gas (Ikramuddin, 2014). The hospital list price for the implant kit is $17,500 (EnteroMedics, 2015b).

EndoBarrier®

The EndoBarrier is intended to function similarly to RYGB without involving fully-invasive surgery. The procedure is typically performed in less than an hour and consists of passing a thin plastic sleeve via the mouth to the small intestine where it is fixed in place by a metal anchor. The sleeve lines the first 60 cm of the small intestine, causing food to be absorbed further down in the intestine. Once implanted, the EndoBarrier influences certain gastrointestinal hormones that play a role in insulin sensitivity, glucose metabolism, and satiety (Rattue, 2012). The device is being investigated for its effects on both weight loss and T2DM. Complications reported in a clinical study included esophageal and pharyngeal tears, sleeve migration, anchor dislocation, sleeve obstruction, and abdominal pain.

Importantly, while the EndoBarrier has been approved for use in Europe, the regulatory approval process in the US has been delayed due to a higher-than-expected rate of bacterial liver infection among patients enrolled in the Phase III trial of the device (Fierce Medical Devices, 2015). As a result, enrollment in the trial has been suspended pending a safety investigation.

Intragastric Balloons (IGB)

There are several intragastric balloons undergoing clinical development, although none are as yet FDA-approved. These include saline balloons such as the BioEnterics® Intragastric Balloon (BIB® or

"Orbera"), the Silimed® Intragastric Balloon ("BIS"), the Spatz3 Adjustable Balloon System, and the ReShape Medical® Intragastric balloon, as well as the air-based Helioscopie Heliosphere® Bag System. The ReShape balloon is currently undergoing FDA review (ReShape Medical, 2014).

Unlike earlier-generation balloon systems, which were intended to be permanent, these systems involve temporary insertion, usually for no longer than six months. The purpose of the balloon is to provide patients with an opportunity to adjust eating habits and make other lifestyle or behavioral changes, or to promote weight loss prior to bariatric surgery. The balloons are inserted in the stomach via endoscopy and then filled with saline or air; removal is also performed endoscopically. The space filled by the balloon is intended to promote earlier feelings of satiety and thereby reduce portion sizes. Reported complications include balloon migration, infection, and bowel obstruction, as well as nausea and vomiting (UK Health Centre, 2015).

Medications

A number of medications have recently been approved for the treatment of obesity or overweight, and these are described in further detail in the sections that follow. All are indicated for use in patients with a BMI ≥30 or in those with a BMI ≥27 who have at least one weight-related comorbidity.

Liraglutide (Saxenda®)

Liraglutide is an injectable glucagon-like peptide-1 (GLP-1) agonist that was previously approved for glycemic control in T2DM under the brand name Victoza® (The Medical Letter, 2015). The version indicated for weight loss involves a higher daily dose (3 mg/day vs. a maximum of 1.8 mg/day for glycemic control). The drug is self-injected daily (Novo Nordisk, 2015). Side effects of liraglutide include nausea, vomiting, constipation, and diarrhea, and the medication has also been found to slow gastric emptying and decrease the rate and/or extent of absorption of other medications (The Medical Letter, 2015). Finally, thyroid C-cell hyperplasia with liraglutide has been reported in animal studies, and the medication carries a "black box" warning because of this (Novo Nordisk, 2015). The annual cost of liraglutide is estimated to be about $12,000 (REDBOOK, 2015).

Lorcaserin (BELVIQ®)

Lorcaserin is a selective serotonin 2C agonist with appetite-suppressant effects. Because of its potential to affect cognition and attention levels, lorcaserin is listed as a Schedule IV controlled substance (US Drug Enforcement Administration (DEA), 2015a). The recommended dose is 10 mg orally twice daily (Arena Pharmaceuticals/Eisai, Inc., 2015). Adverse effects of lorcaserin have included headache, nausea, and dizziness, as well as episodes of euphoria and cognitive/attention disturbance. The label also carries warnings concerning serotonin syndrome or neuroleptic malignant syndrome if lorcaserin is co-administered with other serotonergic agents as well as a

general warning regarding possible development of valvular disorders (Arena/Eisai, 2015). The annual cost of lorcaserin is about $2,400 (REDBOOK, 2015).

Naltrexone/Bupropion (Contrave®) (N/B)

Contrave is a fixed-dose combination of the antidepressant and smoking-cessation agent bupropion as well as the opioid receptor antagonist naltrexone. Unlike lorcaserin, this combination product is not a scheduled controlled substance because it does not have serotenergic effects. Bupropion acts as an appetite suppressant, while naltrexone acts to amplify this effect and reduce food cravings (The Medical Letter, 2015). Each tablet contains 8 mg naltrexone and 90 mg bupropion; dosage escalates over the first month, culminating in a daily dose of four tablets from week 4 onward (Orexigen/Takeda, Inc., 2015). Side effects include nausea, vomiting, headache, constipation, dizziness, and dry mouth. The package insert also contains a "black box" warning regarding suicidal thoughts and neuropsychiatric reactions, both of which have been reported with bupropion use for smoking cessation (Orexigen/Takeda, 2015). The annual cost of N/B is about $2,400 (REDBOOK, 2015). In May 2015, a 9,000-patient clinical trial focused on cardiovascular outcomes was halted upon release of early data from 25% of the accrued sample suggesting a benefit of N/B in reducing major cardiovascular event rates; subsequent release of data from the study executive committee showed no statistically-significant decrease in event rates with data from 50% of participants, however (FiercePharma, 2015).

Phentermine/Topiramate (Qsymia®) (P/T)

Qsymia is a fixed-dose combination of the appetite suppressant phentermine and the anti-seizure medication topiramate (The Medical Letter, 2015). It is a schedule IV controlled substance because of the abuse potential of phentermine (US DEA, 2015b). The medication is available in four dosage strengths, and a dose-escalation schedule is recommended; the maximum daily dose includes 15 mg of phentermine and 92 mg of topiramate in a single tablet (Vivus, Inc., 2015). Side effects may include dry mouth, constipation, disordered taste, paresthesia, and insomnia at higher doses; cognition and attention disturbances have also been reported (The Medical Letter, 2015). While there are no black-box warnings, the use of Qsymia is not recommended in patients with underlying cardiovascular disease (The Medical Letter, 2015). Depending on dosage strength, the annual cost of Qsymia is estimated to range from $2,000 - $2,400 (REDBOOK, 2015).

1.3 Public and Representative Private Insurer Coverage Policies

To understand the insurance landscape for bariatric surgery, weight loss devices, and weight loss drugs, we reviewed the publicly available coverage policies and formularies of the Centers for Medicare & Medicaid Services (CMS), California Department of Healthcare Services (DHCS), Aetna, Anthem, CIGNA, Humana, UnitedHealthcare (UHC), Health Net, and Blue Shield of California (BSCA).

Overall, public and private payers generally cover RYGB, BPD±DS, LAGB, and VSG for patients with a BMI ≥40, or ≥35 with an obesity-related comorbidity. There is some variation among payers as to which comorbidities are qualifying illnesses for patients with a BMI ≥35, but T2DM, cardiovascular disease, cardiopulmonary disease, and hypertension are broadly included. With three exceptions, payers require that patients seeking bariatric surgery have failed prior conservative management, which typically includes documented participation in a physician-supervised diet and exercise program for three to six consecutive months out of the past 18 to 24 months. Humana and Medicare require that patients have failed prior medial management, and Health Net requires patient failure of a reasonable, documented weight-loss attempt. In addition, all payers except for CMS and Health Net require that candidates for bariatric surgery undergo a pre-operative psychological screening to ensure that the patient is capable of providing informed consent and is able to comply with pre- and post-operative regimens.

Of the payers included in our review, only Aetna covers liraglutide, lorcaserin, N/B, and P/T at a non-specialty tier. The drugs are covered for patients with a BMI >30 kg/m^2 or >27 kg/m^2 who meet the following criteria: 1) serious risk factors such as coronary heart disease, dyslipidemia, hypertension, obstructive sleep apnea, or T2DM; and 2) have failed to lose at least one pound per week after six months of a weight-loss regimen that includes diet, increased physical activity, and behavioral therapy. None of the public or private payers surveyed cover vBloc (IGB and DJBL are not yet FDA-approved).

Table 1 on the following page describes general insurer criteria for the bariatric surgeries, weight-loss devices, and weight-loss drugs included in this review. Appendix H contains a more detailed description of public and private insurance coverage policies, along with links to the policies.

Table 1. Coverage Matrix of Public and Representative Private Insurance Coverage Policies

	CMS	Medi-Cal	Aetna	Anthem	CIGNA	Humana	UHC	Health Net	BSCA
Bariatric Surgery									
Adult BMI Criteria	≥35 with comorbidity	>40, >35 with comorbidity	>40, >35 with comorbidity	>40, >35 with comorbidity	≥40, ≥35 with comorbidity	≥40, ≥35 with comorbidity	>40, >35 with comorbidity	>40, >35 with comorbidity	>40, >35 with comorbidity
RYGB	Open Laparoscopic	Covered	Open Laparoscopic	Covered	Open Laparoscopic	Open Laparoscopic	Covered	Open Laparoscopic	Open Laparoscopic
BPD	Not covered	Not covered	Open Laparoscopic	Not covered	Not covered	Open Laparoscopic	Covered	Not Covered	Not covered
BPD+DS	Open Laparoscopic	Covered	Open Laparoscopic	Covered	BMI >50	Open Laparoscopic	Covered	BMI >50	BMI >50
LAGB	Laparoscopic	Covered	Laparoscopic	Laparoscopic	Open Laparoscopic	Laparoscopic	Laparoscopic	Open Laparoscopic	Laparoscopic
VSG	At MAC discretion, Yes in California	Covered	Open Laparoscopic	Open Laparoscopic	Open Laparoscopic	Open Laparoscopic	Covered	Laparoscopic	Covered
Medications									
BMI Criteria	N/A	N/A	>30, >27 w/ risk factors	N/A	N/A	N/A	--	--	N/A
Liraglutide	N/A	Not listed	Covered	Not listed	Not listed	Not listed	Tier 3	Not listed	Not listed
Lorcaserin	N/A	Not listed	Covered	Not listed	Not listed	Not covered	Tier 3	Specialty	Not covered
N/B	N/A	Not listed	Covered	Not listed	Not listed	Not covered	Tier 3	Not listed	Not covered
P/T	N/A	Not listed	Covered	Not listed	Not listed	Not covered	Tier 3	Specialty	Not covered
Devices									
IGB	Not covered	--	Not covered	--	Not covered	Not covered	Not covered	Not covered	--
vBloc	Not covered	--	Not covered	Not Covered	Not covered	Not covered	Not covered	Not covered	Not covered
DJBL	Not covered	--	Not covered	--	Not covered	Not covered	Not covered	--	--

-- = Not mentioned in coverage policy

MAC = Medicare Administrative Contractor

2. Clinical Guidelines

2.1 Guidelines for Adult Care

Endocrine Society (2015)

http://press.endocrine.org

The Endocrine Society recommends that pharmacotherapy be used as an adjunct to diet, exercise, and behavioral modification in patients with a BMI ≥27 kg/m^2 with a comorbidity or BMI >30 kg/m^2. Pharmacotherapy is also appropriate to maintain long-term weight loss in patients meeting the above BMI and comorbidity criteria. Drug therapy should be continued if a patient loses >5% of their body weight by the third month of treatment and discontinued if a patient loses <5% of their body weight or if there are safety or tolerability issues at any time. Patients should be evaluated for the efficacy and safety of their regimens every three months.

Phentermine is not recommended for patients with uncontrolled hypertension or a history of heart disease; lorcaserin is not recommended for patients with cardiovascular disease; and patients with T2DM should be prescribed antidiabetic medications that have been shown to promote weight loss such as glucagon-like peptide-1 (GLP-1) analogs or sodium-glucose-linked transporter-2 (SGLT-2) inhibitors in addition to metformin.

US Department of Veteran's Affairs / Department of Defense (VA/DoD) (2014)

http://www.healthquality.va.gov/guidelines/CD/obesity/

The VA/DoD guidelines recommend bariatric surgery for patients with a BMI >40 kg/m^2 or a BMI between 35 and 39.9 kg/m^2 and one or more obesity-related comorbidities but note that there is insufficient evidence to support surgery in individuals over age 65 or with a BMI <35 kg/m^2. Surgery may be considered to improve obesity-related comorbid conditions in individuals with a BMI >35 kg/m^2.

The guidelines recommend that pharmacological management with P/T, orlistat, or lorcaserin is appropriate as an adjunct to lifestyle change in patients for whom lifestyle change alone has failed to produce adequate weight loss and with a BMI > 30 kg/m^2 or a BMI > 27 kg/m^2 and at least one obesity-related comorbid condition.

American Heart Association / American College of Cardiology / The Obesity Society (AHA/ACC/TOS) (2013)

http://content.onlinejacc.org/article.aspx?articleid=1770219

The AHA/ACC/TOS joint guidelines recommend bariatric surgery for patients who have not responded to previous behavioral modification, with or without pharmacotherapy, with a BMI >40 kg/m^2 or a BMI >35 kg/m^2 and one or more obesity-related comorbidities. No recommendation was made for patients with a BMI <35 kg/m^2 due to a lack of evidence. The societies do not favor one type of surgery over another; instead, they recommend that the decision be made with regard to the individual circumstances of the patient.

The guidelines did not specifically examine the evidence on pharmaceutical approaches to weight loss, but note that, based on expert opinion, medication management may be appropriate as an adjunct to lifestyle intervention for individuals with a BMI >30 kg/m^2 or a BMI >27 kg/m^2 and at least one obesity-related comorbidity.

American Association of Clinical Endocrinologists / The Obesity Society / American Society for Metabolic and Bariatric Surgery (AACE/TOS/ASMBS) (2013)

http://asmbs.org/resource-categories/guidelines-recommendations

The AACE/TOS/ASMBS guidelines state that bariatric surgery is appropriate for patients with a BMI ≥40 kg/m^2 who do not have existing medical complications or for whom surgery would not pose excessive risk. Patients with a BMI ≥35 kg/m^2 may also be eligible in the presence of at least one severe obesity-related comorbidity. The guidelines note that limited evidence suggests that surgery may be appropriate in patients with a BMI from 30 to 35 kg/m^2 who have diabetes or metabolic syndrome. Bariatric surgery to address glycemic control, lipid lowering, or cardiovascular disease risk reduction is not recommended in the absence of the BMI criteria listed above.

The societies do not recommend one bariatric procedure over another due to insufficient evidence in favor of one approach, instead suggesting that the decision be made based on individualized goals, patient preferences, and a personalized risk stratification. Laparoscopic procedures are generally preferred due to lower early postoperative morbidity and mortality. LAGB, VSG, RYGB, and BPD with or without (±) DS are considered to be the primary procedures of interest, though the guidelines recommend that caution should be taken with BPD±DS due to the greater nutritional risks associated with a large length of bypassed small intestine.

2.2 Position Statements

American Society for Gastrointestinal Endoscopy / American Society for Metabolic and Bariatric Surgery Task Force on Endoscopic Bariatric Therapy (ASGE/ASMBS) (2011)

https://asmbs.org/wp/uploads/2011/11/PathwayToEndoscopicBarTherapies-Nov2011.pdf

The ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy (EBT) issued a white paper in 2011 to propose a framework for the development, investigation, and adoption of EBT including intragastric balloon, duodenal-jejunal bypass sleeves, and gastric electrical stimulation devices. An EBT intended for use as a primary therapy should produce a minimum of 25% excess weight loss (EWL) when measured at 12 months. Additionally, studies should demonstrate that the mean percent EWL difference between primary EBT and control groups is at least 15% and statistically significant. These figures may vary for an EBT intended for a non-primary use such as: early intervention, bridge therapy to induce weight loss prior to another bariatric procedure, or to improve metabolic illness. When used as a non-primary therapy, an EBT should produce a minimum 5% total weight loss and exceed the weight loss attainable through medical and lifestyle intervention.

ASMBS (2011)

https://asmbs.org/resources/preoperative-supervised-weight-loss-requirements

In a 2011 position statement, the ASMBS argues that pre-operative diet requirements prior to bariatric surgery are unsupported by evidence and that they are "inappropriate, capricious, and counter-productive." Pre-operative weight loss requirements increase patient health care costs and are an inconvenience to patients due to mandated physician visits that are not covered by health insurance. The ASMBS notes that it may be appropriate for treatment teams to recommend pre-operative weight loss to improve surgical risk and evaluate adherence based on a patient's individual needs, but there is only low-level evidence in support of this practice.

ASMBS (2012)

https://asmbs.org/resources/bariatric-surgery-in-class-i-obesity

This 2012 position statement from the ASMBS states that bariatric surgery should be an option for patients with a BMI from 30 – 35 kg/m^2 whose weight and comorbidities are not substantially and durably improved by non-surgical interventions. The society further states that the current BMI cut-off point for surgery (>35 kg/m^2 with comorbidities, >40 kg/m^2 regardless of comorbidity) "was established arbitrarily nearly 20 years ago," and that "there is no current justification on grounds of evidence of clinical effectiveness, cost effectiveness, ethics, or equity that this group should be excluded from life-saving treatment."

2.3 Selected International Guidelines

Guidelines published by the UK's National Institute for Health and Care Excellence (NICE) are summarized below.

National Institute for Health and Care Excellence, UK (NICE) (2014)

https://www.nice.org.uk/guidance

Bariatric surgery is appropriate for patients with a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 and a significant comorbidity (e.g., T2DM or high blood pressure) that is expected to improve through weight loss. Bariatric surgery should only be pursued in patients for whom all non-surgical approaches have failed, who have been receiving intensive management, are suitable candidates for anesthesia and surgery, and are able to commit to long-term follow-up. An expedited assessment should be provided for patients with recent-onset T2DM and a BMI ≥35 kg/m^2. Recent-onset T2DM in patients with a BMI of 30 to 34.9 kg/m^2 or in individuals of Asian ethnicity at lower BMI thresholds for obesity can also be assessed on an individual basis.

Surgery is generally not recommended for children or adolescents, though exceptional circumstances may supersede this rule for adolescents who have reached or are near physical maturity. A medical assessment that includes genetic screening is recommended to identify rare, but treatable causes of obesity.

NICE recommends that duodenal-jejunal bypass sleeves be used only in the context of research due to a lack of evidence on safety and efficacy.

Pharmacotherapy is appropriate for adults with a BMI ≥ 28 kg/m^2 and at least one comorbidity or a BMI ≥ 30 kg/m^2 who have been unable to attain their weight target or have reached a plateau with lifestyle modification, and should be used as an adjunct to diet, exercise, and behavioral change. Adolescents should only receive drug treatment in the presence of physical or severe psychological comorbidities, and treatment should be administered by a multidisciplinary team that can provide drug monitoring; psychological support; and diet, exercise, and behavioral interventions.

Treatment with orlistat should continue for longer than three months only if the patient has lost > 5% of their body weight, and continuation of medical therapy is appropriate as a strategy to maintain weight loss. NICE has suspended their review of lorcaserin pending submission of a licensing application by the manufacturer and also suspended their review of P/T following a negative opinion of the drugs issued by the Committee for Medicinal Products for Human Use (CHMP). A review of N/B is currently under development.

3. Previous Technology Assessments

3.1 Health Technology Assessments

We identified four health technology assessments evaluating at least one of the interventions of interest for this review, as summarized below.

Agency for Healthcare Research and Quality (AHRQ, 2013):

http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=595&pageaction=displayproduct

The AHRQ review evaluated the comparative effectiveness of bariatric surgery procedures (LAGB, RYGB, VSG, or BPD) for adult obese patients with a BMI of 30.0 to 34.9 kg/m² and a metabolic condition compared to nonsurgical interventions. For LAGB, RYGB, and VSG, there was moderate strength of evidence to show that bariatric surgery procedures were effective in treating diabetes, hypertension, and hyperlipidemia in the short-term. The strength of evidence is low for BPD due to fewer studies and smaller sample sizes, and the evidence is insufficient for comparing the outcomes of multiple procedures directly. There is also a low strength of evidence for adverse events (AEs) associated with all four surgical procedures, and insufficient evidence for determining long-term safety of these procedures in a moderately obese population.

Blue Cross BlueShield Association Technology Evaluation Center (BCBS TEC, 2012):

http://www.bcbs.com/blueresources/tec/vols/27/27_02.pdf
http://www.bcbs.com/blueresources/tec/vols/27/27_03.pdf

There are two technology assessments from BCBS TEC that were published around the same time: one evaluates the effectiveness of bariatric surgery procedures in diabetic patients with BMI of 30.0 to 34.9 kg/m², and the other evaluates all patients with moderate obesity undergoing LAGB. With the exception of RYGB, there is limited evidence demonstrating the effectiveness of bariatric surgery to treat diabetes in moderately obese patients. For those undergoing RYGB, the data are variable but promising to show that remission is achieved in the majority of patients. For those undergoing LAGB, the evidence is lacking in both quality and quantity to determine comparative effectiveness against other bariatric surgery procedures with regards to both weight outcomes and AEs, specifically in the long-term.

Canadian Agency for Drugs and Technologies in Health (CADTH, 2010):

http://www.cadth.ca/media/pdf/H0485_Bariatric_Surgery_for_Severe_Obesity_tr_e.pdf

In a technology assessment focused on the use of bariatric surgery procedures for the treatment of severe obesity compared with standard care (e.g., lifestyle modification) and/or pharmacological therapy, the available evidence suggests (although data from good-quality, long-term randomized controlled trials (RCTs) are lacking) that bariatric surgery appears to be more effective than nonsurgical interventions for treating severe obesity. While RYGB and LAGB have certain tradeoffs with regards to risk of complications and reoperations, diversionary procedures, such as BPD, result in the greatest weight loss relative to other procedures. There was a lack of evidence to determine the effectiveness of VSG. This review also assessed the economic impact of treating patients with severe obesity by means of surgery or standard care and found that surgical intervention is more effective and less costly in patients with a BMI greater than 35 kg/m² and an obesity-related comorbidity or a BMI greater than 40 kg/m². The results also suggest that both a high procedure volume and extensive surgical experience are associated with better clinical outcomes.

California Technology Assessment Forum (CTAF, 2009)

CTAF previously evaluated the evidence on LAGB (2009), VSG (2010), and all procedures in patients with diabetes (2012). Findings are summarized below.

http://www.ctaf.org/reports/laparoscopic-adjustable-silicone-gastric-banding-obesity
http://www.ctaf.org/reports/sleeve-gastrectomy-stand-alone-bariatric-procedure-obesity
http://www.ctaf.org/reports/bariatric-surgery-treatment-type-2-diabetes-mellitus

CTAF found that the effectiveness of LAGB was inferior to that of RYGB. There is some trade-off, however, since RYGB is a more technically-demanding procedure and is associated with longer operating times and hospital stays, as well as higher early complication and reoperation rates. LAGB should remain an option for those who are given appropriate informed consent about the benefits and harms of LAGB relative to RYGB. Evidence on VSG was found to be promising, as it is less invasive than RYGB and BPD, but longer-term outcomes are uncertain. Finally, multiple bariatric procedures were found to significantly increase resolution of diabetes compared to intensive lifestyle and medical therapy. However, diabetes alone is not sufficient to justify surgical intervention as it remains unclear whether the harms of surgery outweigh the benefits of disease remission.

4. Evidence Review (Methods & Results)

4.1. Methods

Scope of the Assessment

The scope for this assessment is described in the sections that follow using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, Settings) framework. Our primary goal was to compare the evidence on clinical benefits and harms for surgical procedures, devices, and medications of interest in this review to that of conventional weight-loss management (i.e., combinations of diet, exercise, and/or behavioral and lifestyle interventions). However, we also included studies that actively compared different types of interventions, both across (e.g., device vs. surgery) and within (e.g., gastric bypass vs. gastric banding) categories where available.

Evidence on clinical benefit and harms was primarily derived from good- and fair-quality RCTs and prospective comparative cohort studies. Retrospective comparative cohort studies were summarized where feasible – particularly for harms data, given the large sample sizes available in these types of cohorts. Finally, case series of >50 patients were considered only for evidence on harms and long-term benefit. Surgical series were limited to those with two or more years of follow-up given the expected maturity of this evidence base. However, given that follow-up for emerging devices and drugs is not yet likely to be adequate to impose such a threshold, and/or is limited by the intervention approach itself (e.g., temporary balloon insertion), we did not impose a strict follow-up limit on these case series.

Analytic Framework

The analytic framework for this evaluation is depicted in Figure 5 on the following page. Because there were expected limitations on the impact of obesity interventions on long-term measures of morbidity, mortality, and health-related quality of life (HRQoL), a series of conceptual links was required to tie shorter-term impact on measures of body weight and resolution of or improvement in key comorbidities to longer-term outcomes.

Population

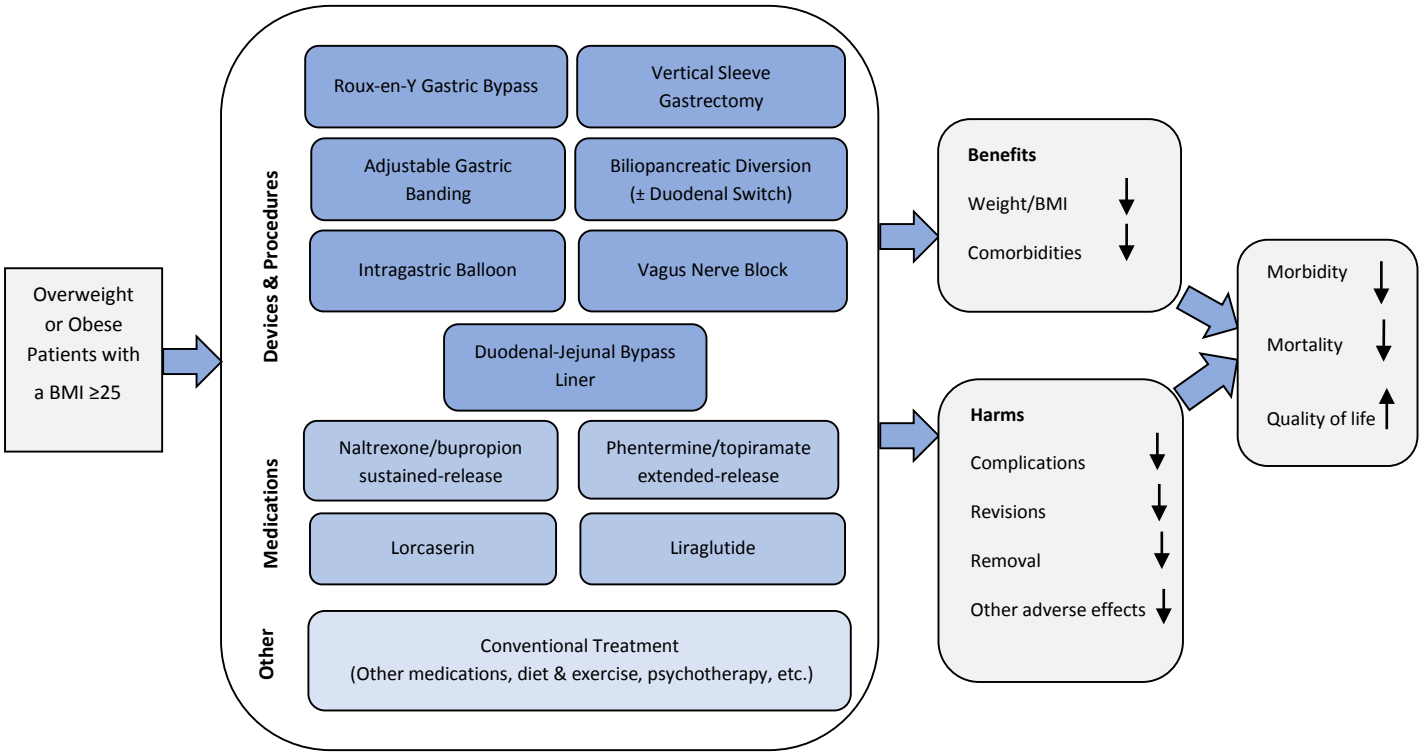
The population of interest included adolescent (i.e., age 12-17) and adult (age 18+) individuals classified as overweight or obese (i.e., BMI ≥25) who received an intervention of interest for this assessment (see "Interventions" below). Studies that focused exclusively on populations with specific conditions (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.

Interventions

For assessment of surgery, studies were limited to those that involve the four bariatric procedures commonly used in the US: Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, vertical sleeve gastrectomy, and biliopancreatic diversion (with or without duodenal switch). We also considered the evidence for three newer types of devices and four medications, as listed below.

Figure 5. Analytic Framework for CTAF Evaluation of Obesity-related Treatments



Devices

- Temporary intragastric balloon systems (e.g., Silimed®, ReShape®)
- Duodenal-jejunal bypass liner (EndoBarrier®)
- Vagus nerve block devices (Maestro® system)

Medications

- Liraglutide (Saxenda®)

- Lorcaserin (BELVIQ®)
- Naltrexone/bupropion sustained-release (Contrave®)
- Phentermine/topiramate extended-release (Qsymia®)

We aimed to focus attention on drugs and devices that have received or are imminently expecting FDA approval. However, while all four medications of interest are FDA approved, only the Maestro device has received such approval. The FDA asked the manufacturer to stop enrollment in the EndoBarrier trial due to a higher-than-expected rate of bacterial liver infection, and the balloons are still undergoing or preparing for FDA review (Fierce Medical Devices, 2015). We nevertheless summarize all available information on these devices to more fully describe the expected landscape for obesity treatment in the near future.

Comparators

Our primary comparator of interest was conventional weight-loss management programs, which may have included combinations of diet, exercise, nutritional and/or behavioral counseling, and medications other than those of focus in our review. We note, however, that many studies compared an intervention of interest to placebo and/or sham devices or to a generalized "usual-care" condition; we abstracted data from these studies as well. Finally, head-to-head studies comparing the interventions of interest were also included for completeness.

Outcomes

Outcomes of interest included the impact of obesity-related interventions on:

- Mortality
- Weight loss related outcomes (e.g., reduction in BMI, % EWL)
- Improvement/resolution of comorbidities
- Measures of pain, function, HRQoL, and/or patient satisfaction
- Short- and long-term complications of surgical procedures and devices
- Reported overall drug-related adverse events (AEs) and AEs leading to discontinuation
- Economic outcomes, including payer costs, patient productivity, and cost-effectiveness

We assessed the evidence on an overall basis as well as stratified by important baseline (e.g., pre-intervention BMI, age, presence of selected comorbidities) and program (e.g., pre-operative weight loss, multidisciplinary care, pre-surgery waiting period) characteristics.

While studies evaluating devices and medications frequently use percent of weight loss or the proportion of patients achieving certain thresholds (e.g., 5-10% reduction in body weight), studies of bariatric surgery instead often report % EWL which represents weight loss that has been achieved relative to a defined goal (i.e., the patient's individualized ideal body weight); these data

are reported according to the study's criteria for determining successful outcomes. Because the range and severity of complications varied between the surgeries and devices, we focused on treatment-related morbidity, mortality, and complications leading to revision, repair, or removal. For medications, the focus of attention was on overall rates of all reported AEs, defined by the FDA as any undesirable experience associated with the use of a medicinal product (FDA, 2015), as well as the proportion of AEs leading to drug discontinuation during follow-up.

Timing

Evidence on intervention effectiveness was limited to comparative studies with at least six months of follow-up as a gauge of the durability of weight-loss and related outcomes. Evidence on harms was derived from comparative studies of any duration, as surgical and device-based interventions report complications at the greatest level of detail during the peri-procedure period (i.e., within 30 days after surgery or minimally-invasive interventions). Evidence on effectiveness and harms from case series focused on studies meeting sample-size and quality criteria (described on page 23).

Settings

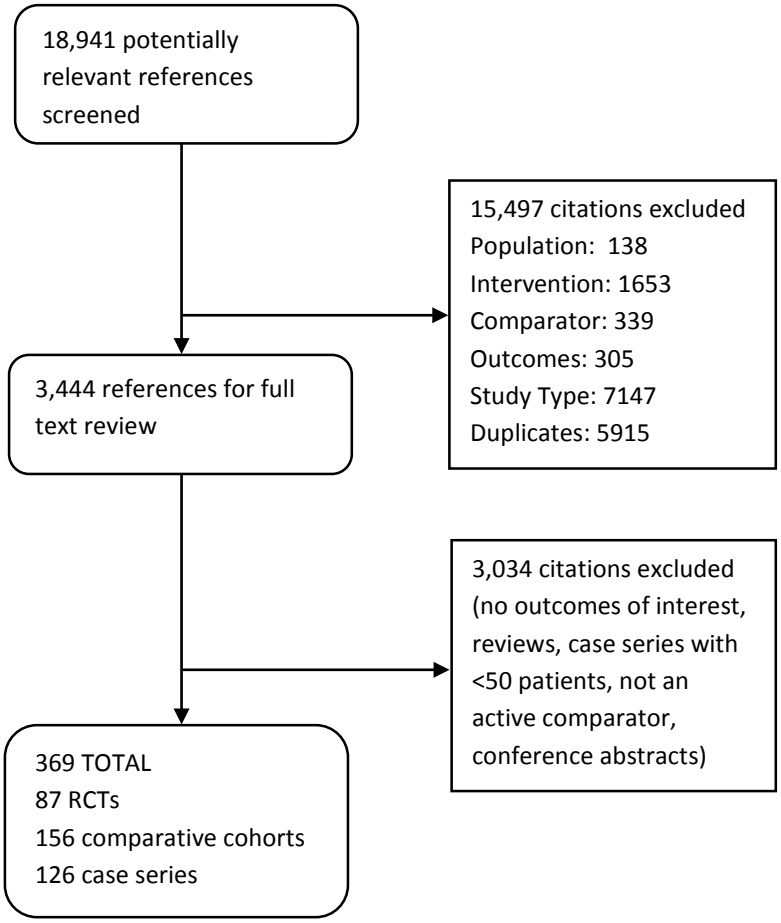
All relevant settings were considered, including inpatient, clinic, and outpatient settings.

Literature Search and Retrieval

The timeframe spanned the period from January 2000 to the most recently published data available. The electronic databases searched as part of the systematic review included MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, PsycINFO, and CINAHL. Electronic searches were supplemented by manual review of retrieved references, previously published technology assessments, and systematic reviews. Further details on the literature search strategy can be found in Appendix A.

The combined search results identified 18,941 potentially relevant studies for this assessment (see Figure 6 on the next page). After elimination of duplicate and non-relevant references, we identified 87 RCTs, 156 comparative cohort studies, and 126 case series, for a total of 369 included studies. The total number of studies for each intervention is as follows: 275 for bariatric surgery, 46 for intragastric balloon, two for vagus nerve block, six for DJBL, 22 for liraglutide (Saxenda®), five for lorcaserin (BELVIQ®), five for N/B sustained-release (Contrave®), and eight for P/T extended-release (Qsymia®).

Figure 6. PRISMA flow chart showing results of literature search



Data Synthesis

Data on relevant outcomes were synthesized quantitatively where feasible. Quantitative evaluation was limited to good- and fair-quality RCTs and prospective cohort studies. Random-effects models were specified and focused on odds ratios (ORs) for binary measures such as comorbidity resolution. Weighted mean differences in continuous variables such as body weight/BMI and QoL were also assessed. Note that, because of expected heterogeneity in patient populations (e.g., BMI levels, comorbidity), study design, duration of follow-up, and other important study characteristics, we did not attempt to conduct network meta-analysis or other forms of indirect comparison across different intervention categories; however, meta-analyses as described above were conducted within intervention categories where feasible. Qualitative evidence tables for all RCTs and comparative cohort studies selected for review can be found in Appendix B.

Study Quality

We used criteria published by the US Preventive Services Task Force (AHRQ, 2008) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor." Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

***Good**: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs. Specifically for this review, attrition did not appreciably differ between study groups (≤20% difference).*

***Fair**: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs. Specifically for this review, differences in baseline characteristics and/or duration of follow-up were allowed only if appropriate statistical methods were used to control for these differences (e.g., multiple regression, survival analysis).*

***Poor**: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality. Nevertheless, we restricted our use of case series to those that met specific criteria, including a minimum of 6 months follow-up, sample size >50 patients, clearly defined entry criteria, and use of consecutive samples of patients.

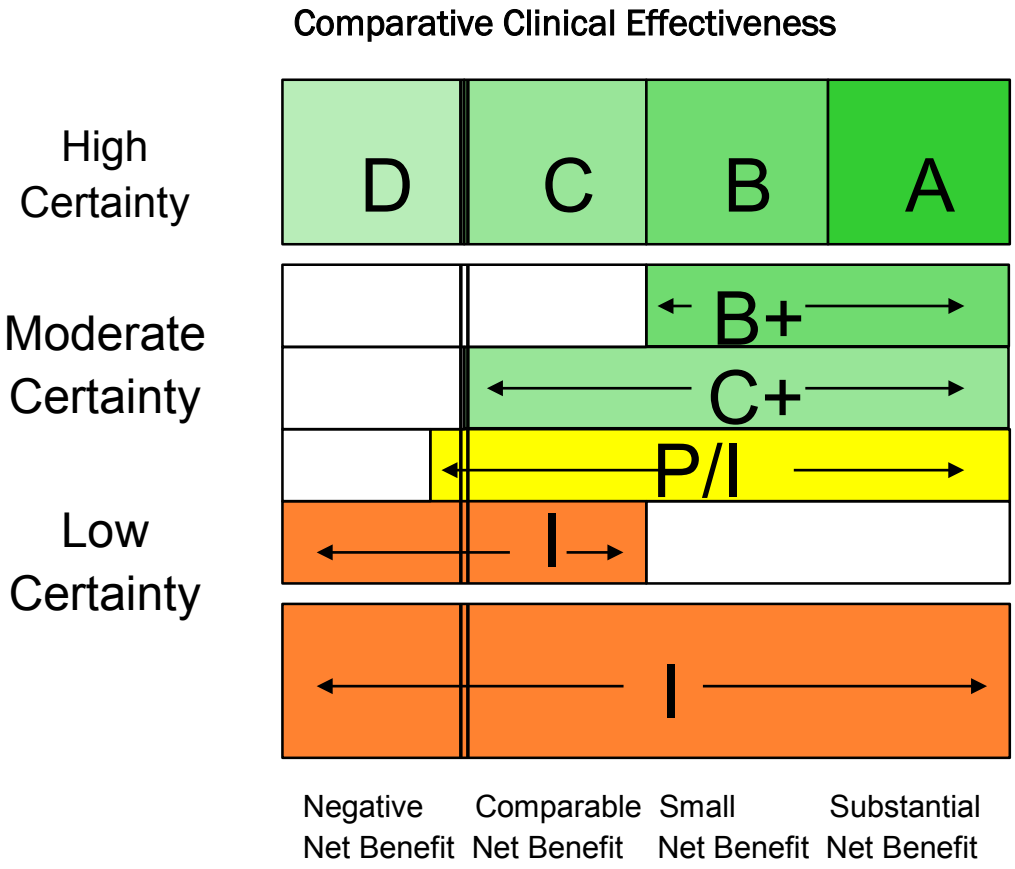
Evidence Ratings

We used the ICER Evidence Rating Matrix to evaluate the evidence for the impact of integrated care on depression, anxiety, QoL, and other outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.

The matrix is depicted in graphic form in Figure 7 below.

Figure 7. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable" - High certainty of a comparable net health benefit
D="Negative" - High certainty of an inferior net health benefit
B+="Incremental or Better" – Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" - Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" – Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

4.2 Overall Evidence Quality

Of the 243 comparative studies identified for this evaluation, we rated only 65 (27%) to be of good quality. An additional 87 studies (36%) were rated fair quality; issues with comparability, duration of follow-up, and/or attrition were identified in these studies, but attempts were generally made to control for confounding in the analytic methods (e.g., survival analysis techniques, multivariate regression). We considered another 91 studies (37%) to be of poor quality because at least one key quality issue was present and not adequately addressed in either study design or analysis, as described further below.

For discussions of evidence, we prioritized all good- and fair-quality RCTs and prospective comparative cohort studies, although good- and fair-quality retrospective cohort studies were also summarized; while not discussed in detail, study characteristics from poor-quality studies can be found in Appendix Table B3. The total number of good- and fair-quality RCTs and comparative cohort studies for each intervention of interest are as follows: 100 for bariatric surgery, 11 for intragastric balloon, two for vagus nerve block, two for DJBL, 19 for liraglutide, five for lorcaserin, five for N/B sustained-release, and eight for P/T extended-release. Importantly, however, many of the medication studies were performed using doses and regimens that are not part of the FDA approval package. For example, only two of the 19 liraglutide studies used the dose that is approved for weight loss. Across all interventions, follow-up was generally limited to 1-2 years in available studies. Only bariatric surgery had a significant number of studies with two or more years of follow-up, but many of these saw high rates of patient attrition over time due to poor post-surgery program adherence. As such, it is problematic to draw firm conclusions from these studies due to the potential for "informed" censoring (i.e., patients with negative outcomes are less likely to be available for long-term follow-up).

We did not identify any studies evaluating patient/program characteristics associated with treatment success for any intervention other than bariatric surgery and intragastric balloon. In addition, bariatric surgery was the only intervention with sufficient evidence to conduct a meta-analysis. Finally, the intragastric balloon studies were highly variable in terms of comparator (different forms of conventional management or bariatric surgery) as well as treatment regimen (e.g., single vs. multiple temporary insertions).

There were specific quality issues with the evidence for surgery and devices. First, treatment groups were often imbalanced with respect to baseline characteristics with the potential to influence outcomes. This was not only frequently encountered but also seldom controlled for in statistical analyses of outcome, even if differences were in baseline body weight or BMI. Another important concern was with follow-up, manifested in both systematic differences between groups in duration of follow-up as well as high rates of loss to follow-up in many long-term studies (due to informed censoring as mentioned above). Large-scale patient attrition is certainly understandable in these

patients, given the clinical complexity involved in obesity-related illness; however, very few studies accounted for patient attrition using well-accepted methods such as survival analysis and/or actuarial reporting.

Finally, most studies were lacking standardized definitions for important outcomes. For example, relatively few surgical or device studies used an accepted classification system (e.g., Clavien) for categorizing the severity of treatment-related complications; we were therefore limited to tracking overall complication rates alone across studies. In addition, definitions of comorbidity resolution varied across studies. For example, resolution of T2DM was determined based on reductions of hemoglobin A1c (HbA1c) below a clinically-important threshold in some studies (the thresholds themselves also varied), and in others, reduction or elimination of diabetes medications was also required.

4.3 Comparative Effectiveness and Safety

Evidence on comparative clinical effectiveness and safety is described separately for bariatric surgery, devices, and medications in the sections that follow. Because evidence in patients with BMI <35 was deemed to be of particular interest, findings for this subpopulation are highlighted separately for each intervention. Of note, although each of the included medications is intended for patients with a BMI ≥30 (or >27 with comorbidities), the mean baseline BMI of patients across studies was approximately 36. As such, evidence of the effectiveness and safety of the medications of interest in patients with lower BMI levels is extremely limited.

Table 2 on the following page summarizes the level of certainty in the evidence according to BMI category, as well as by the presence of T2DM, the comorbidity most commonly studied for BMI levels <30 and 30-34.9. Because uncertainties remain with long-term outcomes and durability of clinical benefit across all interventions, we did not consider the evidence to provide high levels of certainty for *any* intervention. Across interventions, the evidence is strongest for surgery, as well as for all interventions in patients with a BMI ≥35. A detailed summary of the evidence is then described according to intervention type in the sections that follow.

Table 2: Strength of Evidence by BMI Category

BMI	<30		30-34.99		35-39.99	≥40
T2DM	Yes	No	Yes	No	---	---
Bariatric Surgery						
BPD						
LAGB						
RYGB						
VSG						
Devices						
IGB						
DJBL						
vBloc						
Drugs						
Liraglutide						
Lorcaserin						
N/B						
P/T						

Key
No evidence
Low certainty
Moderate certainty
High certainty

4.3.1 Bariatric Surgery

The evidence comparing bariatric surgical procedures to conventional weight-loss management in adult patients is summarized below by key outcome of interest. Because the majority of studies presented outcomes after a minimum of one year, the primary focus of discussion is on good- or fair-quality RCTs and prospective cohort studies with at least 12 months of follow-up, although higher-quality retrospective studies are also discussed in some detail (as these tend to involve larger sample sizes).

Impact of Bariatric Surgery on Overall and/or Cause-Specific Mortality

Importantly, none of the studies in our comparative set directly addressed the impact of bariatric surgery on all-cause or obesity-related mortality; this is not surprising given the significant patient attrition in long-term follow-up for the comparative studies in our sample. A recently-published meta-analysis of long-term data from older trials and cohort studies (published 1986-1997) showed a significantly reduced risk of all-cause mortality from RYGB or LAGB relative to nonsurgical controls (Odds Ratio [OR] 0.55; 95% CI: 0.49, 0.63) and a similarly reduced risk of cardiovascular mortality, but major limitations were noted in the available data, including sample attrition, lack of statistical control for other mortality risk factors, differential ascertainment of causes of death for surgical and

control patients, and a trend toward overstating mortality benefits in smaller studies (Pontiroli, 2011). We did not include the Swedish Obese Subjects (SOS) study in our analytic set because the primary surgical intervention was gastroplasty, which is no longer performed in the US. Long-term follow-up from this study in a matched set of surgical and control patients also suggests that bariatric surgery reduces the risk of all-cause mortality (Hazard Ratio [HR] 0.71; 95% CI: 0.54, 0.92) (Sjöström, 2007). However, the authors note that the recorded death rate was more modest than expected (5% and 6.3% over 15 years for surgical and control patients, respectively), and there was not sufficient discriminatory power in the analysis to ascribe mortality benefit to surgery-induced weight loss.

Other mortality studies were not included in our set because they did not include a comparison to a control group that featured an active comparator; these studies have produced somewhat conflicting results. Adams and colleagues assessed overall and cause-specific mortality over a mean of 7.1 years in nearly 10,000 surgical patients matched to severely obese nonsurgical controls who had applied for driver's licenses in Utah (Adams, 2007). They found significantly reduced rates of mortality from cardiovascular-, diabetes-, and cancer-related causes; however, a key limitation of this study was a lack of information on the baseline health status of control patients. Another large (n=42,094) comparison of bariatric surgery patients and nonsurgical controls treated at 12 Department of Veterans Affairs (VA) centers found a borderline significant reduction in all-cause mortality (HR 0.80; 95% CI: 0.63, 0.995) over a mean of 6.7 years of follow-up (Maciejewski, 2011); however, additional analyses in a subset of patients matched on the propensity score for bariatric surgery failed to yield a statistically-significant result. By contrast, a more recent VA-based evaluation examined all-cause mortality at multiple time points during and up to 14 years of follow-up in 2,500 surgical patients matched on a 1:3 basis to nonsurgical controls (demographics for matched cohorts: mean age 53, 74% male, mean BMI 46) (Arterburn, 2015). No significant differences between groups in all-cause mortality were observed at one year of follow-up. At one to five years, however, surgical patients experienced significantly lower rates of mortality (HR: 0.45; 95% CI: 0.36, 0.56); findings were similar at five to 14 years of follow-up.

Bariatric Surgery vs. Nonsurgical Management: Other Outcomes

We identified a total of 21 reports of good- or fair-quality RCTs (14) and prospective cohort studies (seven) comparing one or multiple forms of bariatric surgery to nonsurgical management. Characteristics of included studies can be found in Appendix Tables B1-B2. Mean age ranged between 41.4 and 57.7 years (average across studies: 46.4); however, most studies had relatively strict age criteria for entry (e.g., 20-50 years), and elderly patients were examined in only two (Halperin, 2014; Scopinaro, 2011). Across all studies, 70-80% or more of subjects were female.

Consistent with the selection criteria for this evaluation, nonsurgical comparators involved some form of active diet, lifestyle, and/or medical intervention. In some studies, the intervention was

labeled “intensive”; this was variably defined, ranging from dietary and exercise therapy in a supervised rehabilitation setting (Karlsen, 2013) to outpatient programs involving behavior modification, medication, and dietary counseling (O’Brien, 2006) to fully-integrated multidisciplinary programs involving physicians, dietitians, psychologists, and occupational/physical therapists (Padwal, 2014).

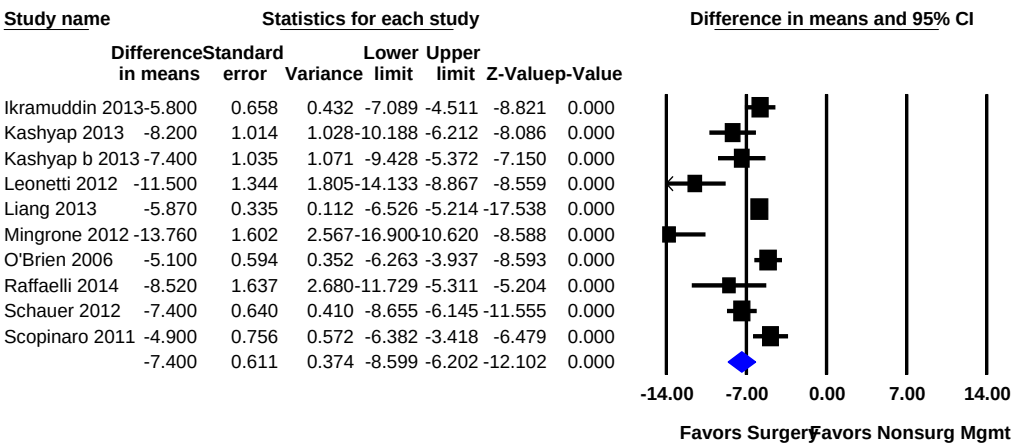
Surgical interventions also varied in these studies. RYGB was assessed in 13 studies, followed by LAGB (6), VSG (4), and BPD±DS (3) (note: some studies involved multiple procedures). In most studies, lifestyle interventions were compared to surgical intervention alone or with limited lifestyle support; in a few, however, the intensive lifestyle intervention was provided to all patients, and surgery was added (Kashyap, 2013; Schauer, 2012 and 2014). Studies were typically performed in all potential candidates for bariatric surgery, but some focused solely on patients with specific comorbidities, typically T2DM (Courcolas, 2014; Dixon, 2008; Halperin, 2014; Ikramuddin, 2013; Leonetti, 2012; Liang, 2013; Mingrone, 2012; Schauer 2012, 2014; Scopinaro, 2011).

Impact on Measures of Body Weight

In comparison to nonsurgical management approaches, bariatric surgical procedures were associated with substantial and statistically-significant improvements in measures of weight change at a median of two years of follow-up, irrespective of the type of procedure performed or the measure of weight change (e.g., change in BMI, percentage of excess and/or total body weight lost, changes in fat mass or waist circumference).

Figure 8 on the next page presents the results of our meta-analysis of mean BMI at study end for the good- and fair-quality studies that produced these measures along with an appropriate measure of variance (e.g., standard deviation, standard error, 95% confidence interval). The pooled mean difference in BMI at study end was 7.4 points (95% CI: 6.2, 8.6). There was a relatively high degree of heterogeneity in these estimates (I2=84%), but in this case the variability is in the degree of treatment effect across studies; the direction of the effect of surgery in reducing BMI is quite consistent across all studies in the analysis.

Figure 8. Meta-analysis of Mean BMI at Study End: Bariatric Surgery vs. Nonsurgical Management



Heterogeneity: Tau^2= 2.81; Q=55.8; df=9; I^2=84%
Test for overall effect: Z=-12.1 (p<0.001)

Impact on Resolution of Comorbidities

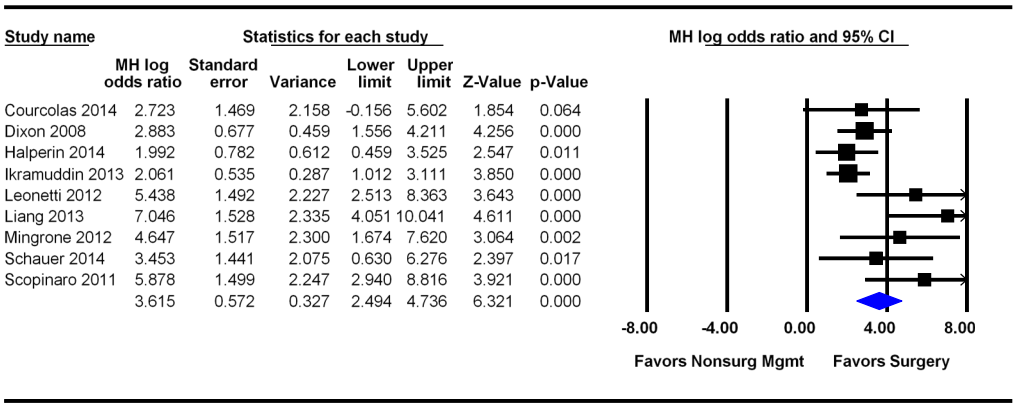
Improvement and/or resolution of comorbidities was reported in 16 of 21 studies (76%); however, in some of these studies, improvement was measured only in terms of mean changes in laboratory parameters. The most frequently-reported comorbidity was T2DM.

Figure 9 on the following page shows the results of our meta-analysis of resolution of T2DM in studies conducted solely in patients with this condition; bariatric surgery was associated with a substantial increase in the likelihood of full resolution (Mantel-Haenzel log OR 3.62; 95% CI 2.49, 4.74).

Two studies examined the impact of bariatric surgery on comorbidity resolution using composite measures. Ikramuddin and colleagues randomized 120 patients (mean age 49, 76% female, mean BMI 35) to receive RYGB or lifestyle medical management (nutritional and exercise counseling, weight-control medications, medication optimization for cardiovascular risk factors) over 12 months of follow-up (Ikramuddin, 2013). The primary treatment goal was a composite of HbA1c <7%, LDL cholesterol <100 mg/dl, and systolic blood pressure <130 mm Hg, and this was reached by 49% of those receiving surgery and 19% in the lifestyle intervention group (OR 4.8; 95% CI: 1.9, 11.7). A two-year RCT assessed the impact of LAGB versus intensive medical therapy (very low-calorie diet, weight-loss medication, and intensive physician and dietary counseling) in 80 patients (mean age 41, 76% female, mean BMI 34) (O'Brien, 2006), and found that LAGB resolved "metabolic syndrome" as defined using Adult Treatment Panel III (ATP III) criteria (i.e., obesity plus at least two

of: hypertriglyceridemia, reduced HDL cholesterol, hypertension, raised plasma glucose) in 14 of 15 patients diagnosed at baseline (93.3%) versus resolution in seven of 15 (46.7%) for the comparison (p<0.002).

Figure 9. Meta-analysis of Resolution of T2DM: Bariatric Surgery vs. Nonsurgical Management



Heterogeneity: Tau^2= 1.58; Q=20.5; df=8; I^2=61%
Test for overall effect: Z=6.32 (p<0.001)

Other individual comorbidities commonly evaluated in these comparative studies included hypertension and hyperlipidemia. In studies evaluating resolution of these conditions and/or discontinuation of relevant medications as a binary variable, bariatric surgery was associated with two- to three-fold reductions in the prevalence of these comorbidities at the end of follow-up, while nonsurgical management resulted in no appreciable change from baseline (Dixon, 2008; Halperin, 2014; Leonetti, 2012; Liang, 2013; Mingrone, 2012; Scopinaro, 2011). Detailed findings are presented in Appendix B.

We identified three good- or fair-quality studies of the effects of bariatric surgery on sleep apnea. One was a good-quality RCT of 60 patients (mean age 49, 82% female, mean BMI 45) who were randomized to receive LAGB or conventional weight-loss treatment (individualized dietary, exercise, and behavior-modification services) and were followed for two years (Dixon, 2012). Sleep apnea, as measured by reductions in the number of events per hour on the Apnea-Hypopnea Index, improved in both groups and did not statistically differ between them. The prevalence of sleep apnea was reduced significantly in 30 patients with T2DM who received VSG and were followed for 18 months in a prospective cohort (from 15% at baseline to 3% at end of follow-up, p=0.03) (Leonetti, 2012); unfortunately, this measure was not reported for the control group receiving intensive medical therapy. Resolution of sleep apnea also did not statistically differ between groups in a prospective

cohort of 179 patients receiving RYGB or one of three nonsurgical options: a residential program, a commercial weight-loss camp, and a hospital outpatient program (Martins, 2011).

The Martins cohort study was also the only comparative study that evaluated the impact of bariatric surgery on asthma or arthritis relative to nonsurgical management (Martins, 2011). Unfortunately, the methods for defining resolution of these comorbidities were not reported; in any event, the rate of resolution of asthma and arthritis did not statistically differ between the RYGB group and any of the three nonsurgical intervention groups.

Retrospective Cohort Studies

We identified a single retrospective cohort study comparing the effects of bariatric surgery to an active form of nonsurgical management, a matched study of 58 patients with T2DM (mean age 52, 59% female, mean BMI 41) undergoing RYGB or receiving medical management (usual care attendance at an endocrinology clinic) over 12 months of follow-up (Dorman, 2012). RYGB was associated with statistically-significantly greater reductions in BMI, HbA1c, and use of lipid-lowering medications relative to medical management, as well as significantly greater resolution of T2DM.

Outcomes in BMI <35

Among our set of good- and fair-quality RCTs and prospective cohort studies, a total of nine enrolled patients with BMI levels <35 (Courcolas, 2014; Dixon, 2007; Dixon, 2008; Halperin, 2014; Ikramuddin, 2013; Kashyap, 2013; O'Brien, 2006; Schauer, 2012; Scopinaro, 2011). Importantly, seven of the 10 studies included presence of T2DM as an entry criterion, one recruited individuals based on the presence of metabolic syndrome, and two had no specific comorbidity-based entry criteria. All studies involved comparisons of surgery to medical/lifestyle management; procedures evaluated included RYGB (6 studies), LAGB (4), VSG (2), and BPD±DS (1). Outcomes for studies with a mean preoperative BMI of 30-34.9 are summarized in Appendix K; patterns of weight loss across procedures were similar to those in studies of patients at higher BMIs.

More broadly, however, all of the seven studies that measured complete T2DM resolution as a binary variable at 12-24 months of follow-up reported substantially and statistically-significantly greater resolution with surgery (range: 26-73%; median 42%) than with nonsurgical management (range: 0-16%; median 9%). Studies that also reported improvement in or partial remission of T2DM (e.g., reduced HbA1c, reduced insulin use) showed between-group differences of even greater magnitude.

An additional RCT evaluated the effects of LAGB versus intensive medical therapy on metabolic syndrome in 80 patients with mild or moderate obesity (O'Brien, 2006) and observed resolution in 93% and 47% for surgery and medical management, respectively

(p<0.002). Finally, another study compared RYGB to lifestyle management in 120 patients (Ikramuddin, 2013) and found that 49% of surgical patients achieved a composite goal of reductions in HbA1c, LDL cholesterol, and systolic blood pressure below common clinical thresholds, versus 19% in the nonsurgical group (p<0.05).

Most of these studies also reported improvements in measures of cholesterol and blood pressure, but these were most commonly reported as mean changes in laboratory parameters rather than as binary measures of resolution. Improvements were also noted in other laboratory measures such as plasma insulin, HOMA-IR (a measure of insulin resistance), and C-reactive protein. However, neither laboratory measurement nor binary assessment of resolution were reported for other obesity-related comorbidities of interest for this assessment such as sleep apnea, arthritis pain and function, and asthma in studies of lower BMI levels.

Impact on Other Outcomes

Two studies reported the impact of bariatric surgery on HrQoL relative to nonsurgical management. One was a prospective cohort study of 139 patients (mean age 45, 70% female, mean BMI 45) who received RYGB or intensive lifestyle intervention (four inpatient rehabilitation admissions totaling seven weeks) and were followed for 12 months (Karlsen, 2013). HrQoL was measured by the SF-36 as well as two disease-specific scales, the Obesity and Weight-Loss Quality of Life (OWLQOL) and Weight-Related Symptom Measure (WRSM) scales. RYGB was associated with statistically-significantly greater improvement than lifestyle intervention on all summary measures from each of these three scales. The other study was a 10-year follow-up of an RCT (O'Brien, 2013) comparing LAGB to intensive medical therapy. Results from this study are discussed on page 36.

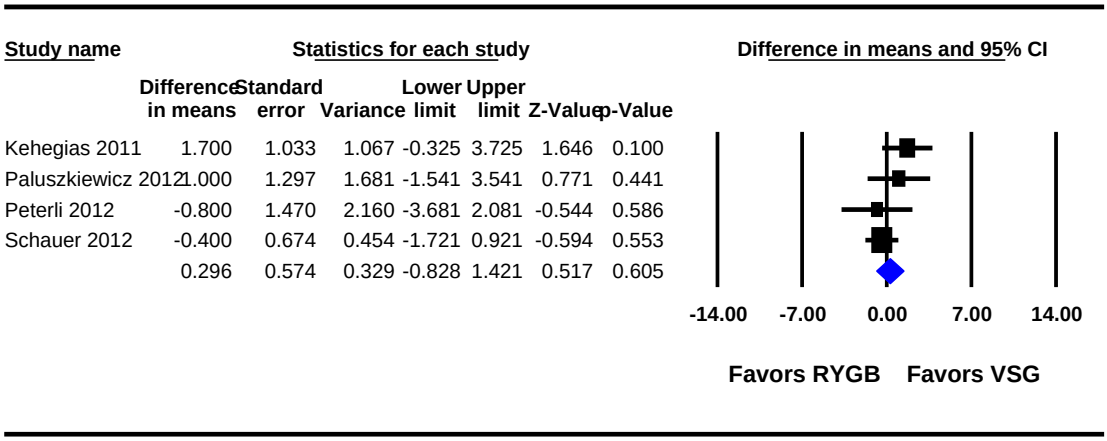
Head-to-Head Comparisons of Surgical Procedures

We identified a total of 24 good- and fair-quality RCTs and prospective cohort studies of bariatric surgery procedures relative to each other with at least 12 months of follow-up. Because the primary comparators of interest in this evaluation were conventional weight-loss management or an alternative treatment approach (e.g., device, new medication), these studies are not discussed in detail here. However, detailed descriptions of findings by procedure type are presented in Appendix G.

The most frequent comparator was RYGB; 12 studies made comparisons to sleeve gastrectomy, seven to gastric banding, and five to biliopancreatic diversion (with or without duodenal switch). Among these procedures, BPD±DS appears to result in the greatest reduction in BMI (median: 24.2; range: 17.9-25.9), followed by RYGB (median: 15.9; range: 10.2-26.8), VSG (median: 13.1; range: 8.9-24.2), and LAGB (median: 9.8; range: 4.8-16.2). Data were sufficient for meta-analysis only for the comparison of RYGB to VSG. As shown below, of the four RCTs of RYGB vs. VSG reporting

difference in mean BMI at study end, no statistically-significant difference in BMI change was observed in any individual study or on a pooled basis. While data were insufficient to conduct meta-analyses on resolution of comorbidities or other outcomes of interest, no differences in outcomes between RYGB and VSG were apparent.

Figure 10. Meta-analysis of mean BMI at study end: RYGB vs. VSG



Heterogeneity: Tau^2= 0.28; Q=3.7; df=3; I^2=20%
Test for overall effect: Z=0.52 (p=0.605)

Findings for all available comparisons of bariatric surgical procedures are described in further detail in Appendix G.

Bariatric Surgery in Adolescents

We found only two studies of sufficient quality demonstrating effectiveness for any bariatric surgery procedure in both children and adolescents: one RCT (O'Brien, 2010) that compared LAGB to conventional weight-loss treatment, and one retrospective cohort (Messiah, 2013) comparing LAGB to RYGB. The RCT (O'Brien, 2010) that involved an obese adolescent population undergoing any bariatric surgery procedure of interest for this review. A total of 50 patients between 14 and 18 years old (mean age 16.6, 69% female, mean BMI 41.4) with comorbidities who were unable to lose weight through conventional methods received either LAGB or lifestyle intervention. The nonsurgical group received an individualized reduced-calorie diet and exercise program, and compliance was monitored via a food diary and step counts on a pedometer. The mean BMI at baseline was higher in the LAGB group, though the difference was not statistically significant (42.3 vs. 40.4 kg/m² for conventional treatment). After two years, the mean BMI was 29.6 kg/m² in the surgical cohort and 39.2kg/m² in the lifestyle intervention group, representing a significantly greater percentage of EWL among those undergoing LAGB (78.8% vs. 13.2%, p<0.001). For those presenting

with metabolic syndrome at study entry, the condition was completely resolved in all nine patients in the surgical cohort compared to six out of 10 patients in the non-surgical group (100% vs. 60%, p=0.025). Mortality was not reported.

Of the five comparative cohort studies we identified in our search, only one study (Messiah, 2013) was found to be of fair quality. The authors retrospectively evaluated 890 obese adolescents from the Bariatric Outcomes Longitudinal Database (BOLD) between the ages of 11 and 19 (mean age 18.5, 75% female, mean BMI 51.4) who received either LAGB or RYGB. Outcomes were assessed every three months up to one year of follow-up. At every time point, patients in both groups had significant weight loss and significant improvement of comorbidities, including T2DM, hypertension, asthma, and obstructive sleep apnea compared to baseline. After one year, patients in the RYGB group lost more than twice as much weight (48.6 vs. 20.0 kg, p<0.001) and had a significantly greater improvement in hyperlipidemia (58.8% vs. 23.3%, p<0.05) compared to those in the LAGB cohort. However, after controlling for selection bias and differences in clinical characteristics between groups at baseline, the mixed model analysis did not yield any significant differences between groups for weight outcomes. There was only one death due to cardiac failure during the study period which occurred in the RYGB group.

Long-term Durability of Treatment Effect

While there are many long-term studies of bariatric procedures, available studies consistently suffer from quality issues that include significant loss to follow-up and a lack of appropriate statistical techniques to account for patient attrition. Many studies examine outcomes of weight reduction, weight regain, comorbidity relapse, and long-term harms only in the patients still enrolled in follow-up programs – populations that likely differ significantly from those who dropped out of the program. Further, analyses conducted at discrete time points discard the information provided by patients who were lost to follow-up between the time points of interest.

We identified 27 good- and fair-quality reports of 22 RCTs, prospective cohort, and retrospective cohort studies; thirteen of the 27 reports were retrospective comparative cohorts and are not discussed in this section. Details of these studies are available in Appendix Tables B1-B2.

Long Term Impact on Measures of Body Weight

We identified 27 reports of 22 good- and fair- quality RCTs and comparative cohort studies that provided data on weight change outcomes beyond two years. Only two RCTs compared bariatric surgery to non-surgical management (O'Brien, 2006; O'Brien, 2013; Schauer, 2012; Schauer, 2014). The first RCT was a three-year study of 137 patients with T2DM (n=137; 66% female; mean age 48.7; mean BMI 36.5) who were randomized to receive intensive medical therapy alone (lifestyle counseling, weight management, home glucose monitoring, and optimized use of anti-diabetic

medications), medical therapy + RYGB, or medical therapy + VSG (Schauer, 2014). After three years, patients lost 24.5%, 21.1%, and 4.2% of total body weight for the RYGB, VSG, and medical therapy groups, respectively ($p<0.001$ for RYGB and VSG vs. medical therapy).

The second study to compare surgery to conventional obesity management was a 10-year follow-up study of 80 patients (mean age 41, 76% female, mean BMI 34) who received LAGB or intensive medical therapy (very low-calorie diet, weight-loss medication, and intensive physician and dietary counseling) (O'Brien, 2006). Although nearly half of those originally randomized to nonsurgical management crossed over to LAGB surgery after the initial two-year trial, patients who did not go on to have the LAGB procedure gained 2.63% excess weight by 10 years, while those who were originally randomized to LAGB lost 63.04% of excess weight ($p<0.05$) (O'Brien, 2013).

The remaining studies evaluated the long-term comparative effectiveness of various bariatric procedures. Angrisani and colleagues randomized 51 patients (mean age 34, 82% female, mean BMI 44) to receive RYGB or LAGB in a single-center evaluation in which patients were followed for five years (Angrisani, 2007); one of the 27 LAGB patients was lost to follow-up during this period. At five years, mean BMI was statistically-significantly lower for RYGB relative to LAGB (29.8 vs. 34.9, $p<0.001$), while the percentage of EWL was significantly greater for RYGB (67% vs. 48%, $p<0.001$). At 10 years, a total of 5/27 LAGB (19%) and 3/24 (13%) RYGB patients were lost to follow-up. Among remaining patients, BMI was essentially unchanged in the RYGB group (30.0 vs. 29.8 at five years), while BMI increased somewhat in the LAGB group (36.0 vs. 34.9 at five years). EWL remained in favor of RYGB (69% vs. 46% for LAGB, $p=0.03$).

Another fair-quality RCT evaluated 111 RYGB and 86 LAGB patients (mean age 43, 77% female, mean BMI 47) who were followed for a mean of 4.2 years at a single bariatric surgical clinic (Nguyen, 2009). Treatment groups were imbalanced because a greater number of LAGB patients could not obtain insurance approval for surgery. EWL was statistically-significantly higher in the RYGB group (68.4% vs. 45.4%, $p<0.05$). In addition, treatment failure, defined as conversion to another procedure because of failure to lose weight or <20% EWL, occurred in 17% of LAGB patients and zero RYGB patients (not statistically tested).

The durability of procedure performance was also examined in the three reports of the Søvik RCT. In the 2010 Søvik study, 60 patients with a BMI of 50-60 kg/m^2 (mean age 35, 70% female, mean BMI 55) were randomized to RYGB or BPD±DS and followed for two years. Mean BMI at 12 months was statistically-significantly lower in the BPD±DS group (32.5 vs. 38.5 for RYGB, $p<0.001$). At 24 months of follow-up, BMI continued to decline in both groups but the magnitude of differences was similar (30.1 vs. 37.5, $p<0.001$) (Søvik, 2011). After five years of follow-up, with a 92% retention rate, the mean BMI for the BPD±DS group remained significantly lower than for the RYGB group (33.1 vs. 41.2 respectively, $p<0.001$), but weight regain (9-10 kg) was comparable for the two groups (Risstad, 2015).

Noticeably missing from weight-change data is any analysis of long-term weight regain following surgery. The SOS study, which followed patients for over 15 years, reported that weight increases did occur 1-2 years after surgery but eventually leveled off. After 10 years, weight loss remained 25% and 14% below baseline weight for the subgroups of patients who underwent RYGB and LAGB, respectively (note that the SOS study was not part of our primary set because a majority of patients underwent gastroplasty, a procedure no longer performed in the US). These results were included in a 2013 systematic review of 16 studies, primarily consisting of case series and cross-sectional surveys (Karmali, 2013). Weight regain was defined variably in these studies, ranging from gains in absolute weight from a nadir value, to gains above a certain kilogram threshold, to reductions in the percentage of excess body weight lost. In most of these studies, weight regain was common, occurring in 70-80% of subjects, but was moderate for most patients (5-10% of original weight loss regained). However, 10-20% of patients also reported weight regain that exceeded predetermined clinically-important thresholds over 1-11 years of follow-up.

Long Term Impact on Resolution of Comorbidities

We found two studies that compared bariatric surgery to non-surgical management with follow-up longer than two years. As described previously, the O'Brien RCT assessed the impact of LAGB versus intensive medical therapy. After an initial two-year study, the authors found that LAGB resolved "metabolic syndrome" as defined using ATP III criteria in 14 of 15 patients diagnosed at baseline (93.3%) vs. resolution in 7 of 15 (46.7%) for the comparison ($p<0.002$). Similar patterns were observed in a 10-year follow-up from this study, although nearly half of those originally randomized to nonsurgical management crossed over to LAGB surgery (O'Brien, 2013).

As with weight changes, degradation in performance of bariatric surgery with respect to comorbidity resolution was rarely evaluated in available RCTs. One RCT (n=150, mean age 48.6, 66% female, mean BMI 36.5) reported achievement of HBA1c levels <6% in 42% and 37% of the RYGB and VSG groups, respectively, versus 12% in those receiving medical therapy alone ($p<0.01$ for both comparisons) after 12 months (Schauer, 2012). Achievement of HbA1c <6% was reduced over the next two year but remained substantially higher in the surgical groups (38%, 24%, and 5% for RYGB, VSG, and medical therapy, respectively, $p\leq0.01$ for both surgeries vs. medical therapy). However, relapse, defined as meeting the HbA1c target and discontinuing anti-diabetic medications at 12 months but not at three years, was also common, occurring in 38% and 46% of RYGB and VSG patients respectively (note: relapse could not be calculated in the medical therapy group because no patients achieved the HbA1c target and discontinued anti-diabetic medications).

Although the results of the SOS study were not included in our meta-analysis, long-term data on T2DM remission are available from this study. While 72% of surgery patients with T2DM experienced remission at two years of follow-up, the rate of relapse among patients with initial

remission and 10 years of follow-up was 50%. Bariatric surgery was associated with reductions in the risk of new-onset T2DM, however (96%, 84%, and 78% after two, 10, and 15 years, respectively) (Sjöström, 2012).

Long Term Impact on Other Outcomes

Limited data were available from RCTs and prospective cohort studies on the long-term durability of other outcomes from bariatric surgery. In the O'Brien study described on page 36 no statistically-significant differences were found between groups in the physical or mental summary component measures of the SF-36 after 10 years follow-up (O'Brien, 2013).

HRQoL was also reported in the Søvik RCT (see Søvik 2010 above) (Risstad, 2015). Although there were statistically-significant improvements from baseline in domain-specific scores of the SF-36 as well as in the Obesity-related Problems Scale, there were no statistical differences between RYGB and BPD±DS groups after five years follow-up.

Long Term Impact in Children/Adolescents

To assess long-term outcomes of bariatric surgery in an adolescent population, we attempted to identify any case series with at least 25 patients and a mean follow-up of least two years with 80% participation at the end of the study. We found only one study (Silberhumer, 2011) that met these criteria. The authors evaluated the clinical effectiveness of LAGB in 50 adolescent patients between nine and 19 years old (mean age 17.1, mean BMI 45.2) over a mean follow-up of slightly more than seven years. At five years, with only 10% lost to follow-up, the mean BMI was 27.3 kg/m², representing a mean EWL of 92.6%, and the difference between time points was significant up to three years ($p<0.01$). All patients with a functional band had 100% resolution of all comorbidities, and QoL after surgery continued to improve over time with significant differences between all points of follow-up up to five years ($p=0.01$).

Harms Associated with Bariatric Surgery

We identified a total of 32 reports of 28 RCTs and prospective cohort studies that met our criteria for good- or fair-quality and reported on harms of the four bariatric surgery procedures of interest for this review. There were seven comparisons involving BPD, 14 of LAGB, 26 of RYGB, and 12 of VSG, with the most frequent comparison between RYGB and VSG. Eight of these studies compared a single bariatric surgery procedure to conventional treatment; although not discussed in detail here, any reported complications, reoperations, or deaths reported in these studies are represented in the overall calculations of harms in Appendix Table D1. The overall complication rate is comparable between RYGB and LAGB (19.4% vs. 17.9% for LAGB), but the reoperation rate is higher for LAGB (14.8% vs. 6.0%), which also has the highest rate of reoperations across all procedures. VSG is associated with the fewest overall complications (9.5%) and reoperations (2.0%),

and BPD±DS has the highest complication rate (31.6%). Most studies were small and too underpowered to detect any statistical differences between procedures for AEs, however. Deaths were rarely or not reported; we identified <100 reported deaths in studies comprising over 30,000 patients. An additional 29 good- or fair-quality retrospective comparative cohort studies were also identified and had outcomes similar to those of the RCTs and prospective cohorts. There is a lack of both short- and long-term data evaluating safety for any bariatric surgery procedure in both children and adolescents.

Table 2 below presents the median overall complication and reoperation rate by procedure across all good and fair quality RCTs and prospective cohort studies regardless of duration. Deaths are reported as absolute values, as they were rarely reported. The detailed findings for each surgical comparison can be found in Appendix Table D1.

Table 2. Median Complication and Reoperation Rates for all Good- and Fair-Quality RCTs and Prospective Comparative Cohort Studies, by Procedure

Procedure	# of Studies	# of Patients	Follow-Up; Range, Median (Months)	Complication Rate; Range, Median (%)*	Reoperation Rate; Range, Median (%)	# of Deaths
BPD	7	189	12-60, 18	17-79, 31.6	3-45, 13.0	0
LAGB	14	13,005	12-120, 24	3-61, 17.9	1-33, 14.8	11
RYGB	26	15,830	1-120, 16	0-78, 19.4	0-33, 6.0	62
VSG	12	2,613	12-36, 12	1-80, 9.5	0-17, 2.0	2

*Complication rate may include reoperations in some studies.

Retrospective Cohort Studies

We identified a total of 59 retrospective cohort studies that reported on harms of surgery. Table 3 on the following page represents the median complication, reoperation and mortality rate across all retrospective comparative studies of good or fair quality (note: some studies involved multiple procedures). Median rates tended to be lower than in RCTs and prospective cohort studies, which is not surprising given the information biases attendant in many retrospective evaluations. Nevertheless, the relative effects between procedures are similar to the prospectively-reported data (see Table 2) with VSG representing the lowest complication rate (8.8%), LAGB with the highest reoperation rate (7.4%), and BPD±DS with the highest overall complication rate (26.9%).

Table 3. Median Complication and Reoperation Rates for all Good- and Fair-Quality Retrospective Comparative Cohort Studies, by Procedure

Procedure	# of Studies	# of Patients	Follow-Up; Range, Median (Months)	Complication Rate; Range, Median (%)*	Reoperation Rate; Range, Median (%)	Mortality Rate; Range, Median (%)
BPD	9	2,659	3-63 (24)	8-83, 26.9	0-30, 3.6	0-2.9, 1.40
LAGB	17	16,335	3-72 (29)	0-53, 10.1	0-44, 7.4	0-2.0, 0.15
RYGB	23	840,895	2-72 (29)	0-78, 9.2	0-22, 5.8	0-4.3, 1.94
VSG	11	16,574	2-63 (23)	0-80, 8.8	0-17, 3.9	0-3.9, 0.07

*Complication rate may include reoperations in some studies.

Case Series

We attempted to identify any case series with at least 100 patients and a mean follow-up of least two years with 70% participation at the end of the study that also reported on harms related to surgery; only 12 studies (two for BPD, seven for LAGB, three for RYGB, and none for VSG) met this criteria for inclusion due to inconsistent reporting of complications and substantial sample attrition. Data abstracted from these studies can be found in Appendix Table D2.

Children/Adolescents

Only two studies (O'Brien, 2010; Messiah, 2013) that met our quality standards reported on harms of bariatric surgery in a pediatric population. The single RCT (O'Brien, 2010) compared 50 patients (mean age 16.6, 69% female, mean BMI 41.4) receiving either LAGB or lifestyle intervention. In the non-surgical group, 11 patients experienced 18 AEs, of which eight were hospital admissions due to depression or hypertension. Twelve patients experienced 13 AEs in the surgical cohort, including nine reoperations (eight revision procedures and one cholecystectomy) and one readmission due to depression. Of the seven patients who withdrew in the lifestyle intervention group, six had gained weight. Only one patient in the LAGB group was lost to follow-up, though the reason is not reported. Mortality was also not reported.

Another comparative cohort study (Messiah, 2013) retrospectively evaluated 890 obese adolescent patients (mean age 18.5, 75% female, mean BMI 51.4) undergoing LAGB or RYGB. The RYGB cohort had 45 readmissions and 29 reoperations, compared to 10 readmissions and eight reoperations in the LAGB cohort. The overall complication rate was 21.6% and 5.0% in the RYGB and LAGB groups, respectively; the majority of complications in both groups were the result of gastrointestinal issues. One death due to cardiac failure during the study period occurred in the RYGB group.

Patient/Program Characteristics Associated with Treatment Success

There are few good-quality comparative studies that stratify outcomes according to various patient characteristics and procedure type. As such, evidence about the differential effectiveness and safety of bariatric surgery procedures according to patient characteristics such as age, gender, race/ethnicity, BMI, or psychosocial factors is inconclusive. Moreover, evidence of the effectiveness of certain programmatic elements, such as participation in mandatory pre-operative weight loss programs and accreditation of bariatric surgery centers, has been largely inconsistent. Nevertheless, there is evidence, albeit limited, that surgeon experience, high procedure volume, multidisciplinary care, adherence to pre- and post-operative follow-up, and post-procedure support may positively influence outcomes. The key factors of each of the studies reviewed for this section are summarized in Appendix C.

Surgeon Experience

The majority of studies that assessed surgeon experience with various bariatric procedures examined the learning curve of individual surgeons or surgical groups. These studies stratified patients into consecutive groups and compared outcomes between the first patients to receive a particular procedure at a single institution with later groups receiving the same procedure. The primary outcomes reported included operative time, complication rate, and length of hospital stay. A large proportion of these studies monitored the RYGB learning curve (n=13), although we did encounter four VSG and two LAGB studies; studies related to surgeon experience with BPD±DS are still lacking.

The range in operative time, length of hospital stay, and complication rate varied widely, and data appeared to be institution-specific in many instances. Because these studies typically reported outcomes from a single bariatric facility and/or a limited number of individual surgeons and had observational study designs, they have limited external validity.

Procedure Volume

The majority of studies assessing outcomes according to surgeon and hospital volume were based on data derived from administrative databases. Several studies aggregated bariatric procedures in their analyses or focused only on RYGB. There is likely bias from unobserved confounding factors in the results of the studies described within this section.

The majority of studies report an inverse relationship between surgeon or hospital volume and AEs. Nguyen et al. (2004) found that in-hospital mortality was lower in academic medical centers with more than 100 RYGB cases per year (0.3%) compared to centers with fewer than 50 cases per year (1.2%, $p<0.01$). This relationship was more pronounced among patients 55 years of age or above, with whom the observed in-hospital mortality was 0.9% at high-volume hospitals and 3.1% at low-

volume hospitals (p<0.01). Likewise, the overall complication rate was significantly lower at high-volume hospitals (10.2% versus 14.5%, respectively; p<0.01) and the mean length of hospital stay was shorter (3.8 versus 5.1 days; p<0.01). Moreover, Nguyen and colleagues found that the mean cost for an RYGB operation was significantly higher at low volume hospitals ($13,908 versus $10,292 for high-volume, p<0.01). Findings were similar in other large studies (Birkmeyer, 2010; Gould, 2007; Murr, 2007; Torrente, 2013; Birkmeyer, 2010; Weller, 2007).

Despite the evidence that higher procedure volumes produce better results, Livingston et al. caution that many of these studies rely on statistical methods that amplify the effects (Livingston, 2007). Specifically, the authors used Monte-Carlo simulated data to demonstrate that as sample size decreases as a result of low-volume, the uncertainty of the true mortality rate as estimated from the observed mortality rate increases. Relatively few extra deaths in low-volume facilities can result in significant volume effects when analyzed with chi-square tests or logistic regression analysis. Furthermore, the logistic regression models employed in volume studies tend to rely on patient data with incomplete clinical information. Models that incorporate "high-fidelity disease-specific clinical information" allow for high quality risk adjustment, after which volume-outcome relationships may disappear (Livingston, 2007).

Multidisciplinary Care

A multidisciplinary care approach has become a common element of bariatric surgery, both before and after the procedure, though very few studies have examined the differential effectiveness of multidisciplinary care across the various bariatric procedures. We found a single study that compared outcomes between patients who received care through a multidisciplinary team approach with those that were treated and followed by the surgical team alone (Chen, 2012). In this study, 200 patients (mean age 31, 62% female, mean BMI 43 kg/m^2) were followed for up to 12 months. At 12 months, the percentage of overall weight loss was statistically significantly greater among patients treated by a multidisciplinary team as compared to two cohorts treated by a single surgical group (mean % weight loss 74.3% vs. 59.8-65.0%, p=0.008). Operative time, hospital length of stay, and overall complications were also statistically significantly lower in the multidisciplinary care group. The researchers credited these improved outcomes to a specialized dietician who met with patients preoperatively and at consistent post-operative follow-up appointments to evaluate and educate patients on their eating patterns and lifestyles. Additionally, the authors suggested that by sharing perioperative care tasks, surgeons were given more time to focus on improving their technique and gaining experience.

In an additional study of 1,236 consecutive LAGB patients in France (49% age 15-39 years, 29% age 40-49 years, 65% BMI 40-49 kg/m^2, % female not reported), authors found that patients who did not change their eating habits after surgery were 2.2 times less likely to have weight loss success (defined as EWL >50% at 2 years post-surgery; p=0.009), and patients who did not recover or

increase their physical activity were 2.3 times less likely to have success (p<0.001) (Chevallier, 2007). Although they did not directly measure the effects of a multidisciplinary care team, the authors emphasized that these findings were indicative of the need to employ a multidisciplinary care team before and after the operation (Chevallier, 2007).

Type of Pre-procedure Preparation/Post-procedure Support

Patient adherence to pre- and post-operative programs and follow-up has been shown to be an important predictor of % EWL. In a subgroup analysis of 177 LAGB patients, those who missed more than 25% of their pre-procedure appointments lost 23% EWL at 12 months compared with 32% for those who missed fewer appointments (p=0.01) (El Chaar, 2011).

Not surprisingly, program adherence after surgery has also been shown to be one of the most important predictors of treatment success. In a study comparing 32 RYGB patients who completed 12 months of follow-up to 28 patients who did not (mean age 46.8, 72% female, mean BMI 52 kg/m^2), Compher and colleagues (2012) calculated that the odds of >50% EWL increased 3.3-fold with each unit increase in the number of follow-up visits (95% CI 1.6, 6.8) and 2.8-fold at 24 months (95% CI 1.4, 5.7). Gould and colleagues (2007) had similar findings after following gastric bypass patients 3-4 years post-operatively. The authors found that patients who attended all scheduled post-operative appointments achieved greater EWL (mean of 70% vs. 60% for those followed for only one year, and 56% among those lost to follow-up before one year; p<0.05). Correspondingly, adherence to scheduled follow-up visits and compliance with recommended post-operative care predict a greater decrease in BMI during the first four years after LAGB[1] (Pontiroli, 2007).

Additionally, there is some evidence that post-operative support groups help patients to make positive lifestyle changes, improve psychological comorbidities, and achieve greater weight loss. Post-operatively, support groups have been associated with greater weight loss success and a reduction in patients' depressive mood (Nijamkin, 2013; Nijamkin, 2012; Elakkary, 2006). In an RCT by Nijamkin and colleagues, 144 Hispanic-American RYGB patients (mean age 44.5, 83% female, mean BMI 49 kg/m^2) were randomized to receive either comprehensive nutrition and lifestyle support or brief, printed healthy lifestyle guidelines six months after surgery (Nijamkin, 2012). At 12 months post-surgery, patients in the comprehensive support group experienced greater EWL (80% versus 64%; p<0.001) and BMI reduction (6.48 vs. 3.63, p<0.001) (Nijamkin, 2012).

Overall, we judge there to be moderate certainty of at least a small-to-moderate net benefit for bariatric surgery over nonsurgical management in individuals with a BMI ≥35. There is moderate certainty of benefit because although there is a fairly large evidence base demonstrating substantial and significantly greater reductions in weight as well as improvements in comorbidities (particularly

[1] Study only reported p-values and f-values; both were significant.

T2DM), studies evaluating the long-term durability of these effects are less robust. The small-to-moderate effect size represents the tradeoffs between the substantial benefits of surgery and the potential for serious complications from all of these procedures. Certainty in these effects also differs by procedure – in these patients, the evidence base is relatively robust for LAGB, RYGB, and VSG, but is smaller and of lower certainty for BPD±DS.

Summary: Bariatric Surgery

For patients with a BMI of 35 and above with or without clinical comorbidities, we judge there to be moderate certainty of a substantial net health benefit of bariatric surgery compared to nonsurgical management; certainty remains moderate because of a lack of long-term data on durability of benefit. For individuals with a BMI 30-34.9, we judge there to be moderate certainty of a small-to-moderate net benefit of bariatric surgery compared to nonsurgical management only among patients with T2DM who receive RYGB or LAGB procedures. The evidence base provides low certainty for all other procedures and for any surgery in this BMI range in patients with comorbidities other than T2DM. Our judgement of the net benefit of bariatric surgery relative to nonsurgical management in pediatric populations is ”insufficient”, as we found only one good-quality RCT of 50 patients that evaluated outcomes in this population. Finally, we found no evidence of the effectiveness of bariatric surgery in patients with a BMI <30.

Across a range of procedures, study designs, and duration of follow-up, bariatric surgery results in greater sustained weight loss (on average, 7-8 BMI points, or 30-40% of total body weight) and resolution of comorbidities (primarily T2DM) than nonsurgical management. The level of certainty in these results is limited by a lack of good-quality long-term data on durability of benefit. There is also a lack of both short- and long-term data demonstrating effectiveness for any bariatric surgery procedure in both children and adolescents. There is little to distinguish performance of individual bariatric procedures, as LAGB use has declined substantially, BPD±DS is technically complex and performed only at certain centers, and the performance of RYGB and VSG is similar.

Evidence on the differential effectiveness and safety of bariatric surgery procedures according to patient characteristics such as age, gender, race/ethnicity, BMI, or psychosocial factors is largely inconclusive. Nevertheless, there is evidence, albeit limited, that surgeon experience, high procedure volume, multidisciplinary care, adherence to pre- and post-operative follow-up, and post-procedure support may positively influence outcomes.

4.3.2 Devices

Intragastric Balloon (IGB)

Intragastric Balloon vs. Conventional Management

We identified a total of seven reports of good- or fair-quality RCTs (five) and comparative cohort studies (two) comparing intragastric balloon to conventional management of obesity. Mean age ranged between 31 and 48 years (average across studies: 39.4), and patients were primarily female (range: 53-80%). Mean BMI across all studies was 41.8, and only two studies allowed participants with a BMI <35 (Fuller, 2013; Ponce, 2013).

Consistent with studies for bariatric surgery, conventional approaches involved some form of active diet, lifestyle, and/or behavioral modification intervention. We did not find any studies directly comparing the intragastric balloon to any form of medical management, including those interventions of interest to this review, although drug therapy for weight loss was permitted as part of the standard treatment group. Only one study (Genco, 2010) had more than six months of follow-up after IGB removal, and two studies included a cohort that received two consecutive temporary balloons (Genco, 2010; Genco 2013).

Impact on Measures of Body Weight

Of the available RCTs, four and one were good- and fair-quality respectively (Fuller, 2013; Genco, 2008; Konopko-Zubrzycka, 2009; Ponce, 2013; Genco, 2010) and measured weight outcomes for IGB compared to conventional approaches. A good-quality RCT (Fuller, 2013) assigned 66 patients (mean age 46, 67% female, mean BMI 36.4) with a diagnosis of metabolic syndrome to receive 12 months of behavioral modification based on a T2DM lifestyle intervention program; the balloon was implanted in 31 of these participants. At time of removal, those subjects undergoing IGB therapy had a statistically-significantly greater reduction in BMI at six months (5.1 kg/m² vs. 1.7 kg/m² for behavioral modification group, $p<0.0001$), although reductions were modest in comparison to bariatric surgery. Weight regain was observed in the IGB group at 12 months, but BMI changes remained in favor of the balloon (-3.4 kg/m² vs. -1.9 kg/m², $p=0.01$). Two additional good-quality RCTs (Ponce, 2013; Konopko-Zubrzycka, 2009) with a total of 66 patients, found statistically-significantly greater percentages of weight loss three months after balloon removal (5.4-11.9%) compared to diet and exercise alone (2.1-4.6%).

Two additional RCTs (Genco 2010; Genco, 2013) evaluated the use of two consecutive balloons compared to diet alone in patients with a BMI of 40-49.9 kg/m². In both studies, all patients initially received IGB therapy for six months, followed by a second balloon for an additional six months with a one-month interval between placements. The first RCT (Genco, 2010) included 100 patients (mean age 32, 80% female, mean BMI 42.8) and found no significant difference in BMI after the first

balloon placement but a significantly lower mean BMI than those in the diet group after the second placement (33.1 kg/m² vs. 37.1 kg/m², p<0.05). After two years of follow-up, weight regain occurred in both groups but differences remained in favor of IGB. The second RCT (Genco, 2013) included 50 patients (mean age 32, 77% female, mean BMI 42.0) and also found no differences between groups at six months, but at 13 months the patients receiving a second balloon had a significantly lower BMI (30.9 kg/m² vs. 35.1 kg/m², p<0.005).

A small, fair-quality prospective cohort study (Takihata, 2014) of 16 patients (mean age 44, 56% female, mean BMI 46.9) was the only study in our set that did not find any significant differences between groups for weight outcomes after six months of therapy with IGB or intensive lifestyle modification. However, the study may have been underpowered to detect body-weight changes given the small sample size.

Impact on Resolution of Comorbidities

Improvement and/or resolution of comorbidities with IGB therapy were not reported in any good- or fair-quality RCTs or prospective comparative cohort studies.

Retrospective Cohort Studies

We identified only one large, fair-quality retrospective cohort (Genco, 2008) with 260 patients (mean age 37.9, 77% female, mean BMI 42) who received either IGB or a structured diet and behavioral modification program; it found that the mean BMI at balloon removal was significantly, albeit modestly lower in the IGB group vs. controls (35.4 kg/m² vs. 38.9 kg/m², p<0.01). Although data for weight outcomes were not reported after the active treatment period, the authors noted that patients in the IGB cohort began to regain weight after 24 months, whereas those in the diet group had already regained any weight they lost while on active treatment. More patients in the IGB group also had resolution of T2DM (39% vs. 28%), hypertension (46% vs. 36%), and joint disease (37% vs. 25%) compared to those in the diet group after 24 months, but these results were not tested statistically.

Outcomes in BMI <35

We did not identify any good- or fair-quality RCTs or comparative cohort studies that included patients with a mean BMI under 35.

Impact on Other Outcomes

Two good-quality RCTs were available to assess the comparative impact of IGB relative to conventional management for QOL measures. The first (Fuller, 2013) assessed QoL in 66 subjects (mean age 46, 67% female, mean BMI 36.4) based on the Impact of Weight on Quality of Life

(IWQOL)-Lite form and found a significant difference in favor of the balloon group at six months, which was maintained through the next six months following removal. Another RCT (Ponce, 2013) evaluated QoL using the SF-36 Form and reported a substantial improvement for IGB in all measures of physical functioning but did not test these results statistically.

Intragastric Balloon vs. Bariatric Surgery

We found a total of four good- or fair-quality comparative cohort studies evaluating balloon versus bariatric surgery on measures of body weight and comorbidities, two of which were prospective (Peker, 2011; Tayyem, 2011) and compared IGB to LAGB. One of these studies (Tayyem, 2011) assessed the impact of these interventions on QoL outcomes. Two fair-quality retrospective cohort studies also compared IGB to LAGB and RYGB (Alfa Wali, 2014) and to VSG (Genco, 2009).

Impact on Measures of Body Weight

We identified two prospective studies (Peker, 2011; Tayyem, 2011) that met our quality criteria. Both were comparisons of IGB to LAGB. One of these was a good-quality prospective cohort study (Peker, 2011) evaluating 32 patients (mean age 35, 75% female, mean BMI 38.3) who received two consecutive balloons or underwent LAGB surgery, with outcomes reported every six months up to 18 months of follow-up. Although results were comparable for weight outcomes at six months, differences in mean BMI (27.5 kg/m² vs. 36.6 kg/m² for LAGB) and % EWL (70% vs. 57% for LAGB) were statistically significant in favor of IGB after one year ($p<0.05$), but differences were no longer significant by the end of the study. A fair-quality prospective study (Tayyem, 2011) included 47 subjects (mean age 40.4, 73% female, mean BMI 56.2) who also received the balloon or LAGB surgery. In contrast to Peker et al., mean BMI was significantly lower (39.7 kg/m² vs. 52.1 kg/m², $p<0.001$) and % EWL was significantly greater (44.0% vs. 26.2% for IGB, $p=0.004$) for LAGB at 14 months.

Impact on Resolution of Comorbidities

Both prospective studies (Peker, 2011; Tayyem, 2011) also evaluated resolution and/or improvement in comorbidities for IGB versus LAGB. Due to the small sample size, Peker et al. presented data on comorbidity resolution and improvement as absolute numbers rather than as a proportion of patients achieving these outcomes and did not test for statistical differences. Tayyem and colleagues did statistically test for differences in comorbidity resolution but did not find any significant differences for resolution or improvement in T2DM, hypertension, hyperlipidemia, or sleep apnea.

Retrospective Cohort Studies

We also identified two retrospective cohort studies, both of fair quality. The largest of these studies (Alfa Wali, 2014) evaluated 983 patients (mean age 48, 79% female, mean BMI 47.5) and found that RYGB was significantly more effective compared to either LAGB or IGB for % EWL after one year (71%, 27%, and 9% for RYGB, LAGB, and IGB, respectively, p<0.001), and continued to be more effective than the balloon up to two years of follow-up (81% vs. 12% EWL for balloon, p=0.05). In addition, although weight loss was similar for LAGB and IGB at one year, % EWL for LAGB was significantly greater than IGB after two years (44% vs. 12%, p=0.05). Genco et al. (Genco, 2009) assessed weight outcomes for 120 patients (mean age 41, 70% female, mean BMI 54.5) and did not find any statistically-significant differences between VSG and IGB patients after one year. The authors noted, however, that after removal of the balloon, patients in the IGB cohort started to regain weight while those in the VSG group continued to lose weight; results were not reported beyond 12 months of follow-up.

Outcomes in BMI <35

We did not identify any good- or fair-quality RCTs or comparative cohort studies that included patients with a mean BMI under 35.

Impact on Other Outcomes

We found only one study (Tayyem, 2011) that evaluated QoL for patients receiving IGB or bariatric surgery (LAGB in this instance). Although participants in both groups reported similar improvements of QOL for all domains from baseline, those in the LAGB cohort reported significantly greater improvements in SF-36 questionnaire scores for physical functioning (89 vs. 75, p=0.025), general health (80 vs. 73, p=0.011), and pain (82 vs. 70, p=0.024) relative to the IGB group.

Long-term Durability of Treatment Effect

No RCTs or comparative cohort studies evaluated outcomes beyond one year of follow-up after IGB removal, so we were unable to assess the long-term impact of the balloon relative to other treatments for obesity. Nevertheless, shorter-term data from these studies suggest that there is a tendency to regain weight when the balloon is removed after six months. Most long-term studies included at least some proportion of patients who had two or more consecutive balloons, had a single balloon longer than six months, or underwent a bariatric surgery procedure within the selected timeframe; these were excluded from our analysis as they are more likely to favor IGB. Table 4 on the following page provides details on the only two long-term case series that met our inclusion criteria on the durability of treatment effect.

Table 4. Long-term Data on Weight Outcomes for Intragastric Balloon

Study	# patients @ baseline	Mean baseline age/BMI	# of patients at @ last point of follow-up	Last point of follow-up (months)	Mean BMI @ balloon removal	Mean BMI @ last point of follow-up
Benamouzig 2013	67	38.9/36.6	29	53	32.2	33.4
Kotzampassi 2012	474	39.4/43.7	195	60	31.9	39.3

Harms Associated with the Intragastric Balloon

As with the other interventions in this assessment, reporting of harms is highly variable for IGB therapy. The most frequently reported complications are nausea, vomiting, and abdominal pain; balloon migration or deflation is infrequent, and the balloon usually passes through the intestinal tract without injury. Early removal of the balloon can occur for any number of reasons, including patient preference (i.e., not safety-related), but is often due to balloon intolerance (e.g., persistent vomiting despite treatment). More serious complications, including gastric perforation or ulcers, bowel obstruction, and esophagitis, are rare.

Table 5 below summarizes the incidence rate for the most frequently-reported complications associated with balloon therapy across all comparative cohort studies of any quality. We did not identify any long-term case series that reported complications after removal of the balloon. Some patients may have experienced more than one symptom or complication; data are reported on a per-patient basis wherever possible.

Table 5. Harms Associated with Intragastric Balloon

Complication	*Nausea/vomiting/ abdominal pain*	*Device migration/deflation*	*Early removal*
# of studies reporting outcome	7	1	5
Incidence rate (range, median)	19-98%, 37.8%	25.8%	2-20%, 8.7%

To further our understanding of the harms associated with the balloon, we identified a systematic review and meta-analysis of RCTs involving a total of 395 patients from the Cochrane Collaboration that evaluated the relative risk of developing complications from temporary IGB therapy relative to diet or no treatment (Fernandes, 2007). Complications found to be significantly associated with IGB included gastric erosions (RR 9.78, 95% CI: 3.87, 24.69) and abdominal pain (RR 14.00, 95% CI: 3.45, 56.74). Other complications under consideration were vomiting and migration/deflation of the balloon; data from these studies did not indicate a statistically-significant difference between

interventions for these outcomes, however. The authors also evaluated early removal of the balloon but a meta-analysis was not conducted.

Patient/Program Characteristics Associated with Treatment Success

No RCTs or comparative cohort studies evaluated patient or program characteristics associated with treatment success in individuals undergoing IGB treatment for obesity. We did, however, find 20 case series of IGB patients that met our inclusion criteria; results from selected case series are summarized as follows. One series (Mathus-Vliegen, 2015) of 815 patients (mean age 37, 84% female, mean BMI 38.1) evaluated the influence of comorbidities and found that the presence of T2DM was associated with a lower rate of successful weight loss (defined as losing ≥10% of initial weight) (1.8% vs. 5.9% without T2DM, p=0.015); findings were similar for patients with osteoarthritis (7.2% vs. 16.8%, p=0.002). Another study (Melissas, 2006) assessing 140 patients (mean age 38, 76% female, mean BMI 42.3) found that the duration of balloon therapy was associated with greater reductions in weight. Those with successful outcomes (defined as ≥25% EWL) had the balloon implanted a median of 206 days compared to those who were considered "failures" (median 187 days, p<0.001). Two other studies (Datsis, 2009; Lecumberri, 2011) found similar results for duration of balloon treatment, but statistical testing was not performed. Data on the influence of age, gender, BMI, other comorbidities, smoking status, psychosocial health, and presence of an eating disorder (e.g., binge-eating) were limited or inconsistent in these studies.

Summary: Intragastric Balloon

We judge there to be low certainty of a comparable net benefit for temporary IGB insertion relative to either lifestyle intervention or bariatric surgery in patients with a BMI ≥35. In comparison to lifestyle interventions, IGB therapy appeared to provide modest reductions in weight across studies, but data on weight change were mixed after balloon removal, there was variability in balloon duration and number of placements, and there is the potential for harm. Evidence of benefit was truly mixed in available comparisons of IGB to bariatric surgery. Evidence on the benefit of the balloon in patients with a BMI <35 or its impact on any other outcome is insufficient to draw any firm conclusions.

Temporary IGB insertion was associated with statistically-significant improvements in measures of weight change at a median of one year of follow-up relative to conventional approaches (e.g., diet, exercise, behavioral modification). Benefits were modest, however – higher-quality studies showed incremental BMI changes and percentage weight loss of 1-3 points and 4-8%, respectively – and also tended to worsen after balloon removal (typically after six months). Certainty was low because of great variability in study design, duration of follow-up (particularly after balloon removal), and treatment approach (i.e., single vs. multiple balloon insertions).

Evidence comparing IGB to bariatric surgery was mixed; several studies showed greater weight loss with IGB vs. LAGB, but differences diminished with greater duration of follow-up. Data are limited on all other outcomes, including resolution of comorbidities and QoL, and in populations with a BMI less than 35. Although there is insufficient evidence on the long-term durability of treatment effect or safety of IGB therapy following balloon removal, weight regain appears to be common, and major treatment-related complications are rare.

Duodenal-Jejunal Bypass Liner *(EndoBarrier®)*

Impact on Measures of Body Weight

We found one good-quality RCT that evaluated the DJBL and met our inclusion criteria. In this study, 73 diabetic patients (35.7% female; mean age 37; mean BMI 35.7) followed a calorie-restricted diet alone or in combination with an implanted DJBL (Koeshestanie, 2014). After six months, the DJBL was removed and all patients were followed for a subsequent six months while maintaining diet and exercise. At month 12, the percent total weight loss was 5.8% in the DJBL group versus 3.5% in the control group ($p<0.05$). Differences in BMI were not statistically significant between groups.

A second fair-quality RCT randomized 41 patients (75.6% female; mean age 41; mean BMI 49) to be implanted with the DJBL and/or to follow a low calorie diet (Schouten, 2010). After 12 weeks, differences in BMI were not statistically significant between groups. A notable limitation of this study, however, was that only three patients kept the device for a full 24 weeks. As discussed in further detail below, safety concerns and complications related to the device led to early explantation of the DJBL in the majority of patients.

Impact on Resolution of Comorbidities

Both RCTs of interest evaluated the impact of the DJBL on improvement or remission of T2DM. Schouten and colleagues observed that after 12 weeks, five (62.5%) of eight diabetic DJBL patients decreased insulin dosages and/or anti-diabetic medication, while one patient discontinued medication altogether; outcomes in the two control patients with T2DM were not reported (Schouten, 2010). Koehestanie and colleagues reported that after one year, 3.3% of DJBL patients discontinued use of metformin, 13.3% discontinued sulfonylurea derivatives, and 13.3% discontinued insulin; similar percentages of control patients discontinued metformin (2.6%) and sulfonylureas (13.9%), but no control patients discontinued insulin (Koehestanie, 2014).

Outcomes in BMI <35

We found no studies that had a patient population with mean BMI <35 and met our inclusion criteria.

Impact on Other Outcomes

We found no studies that reported other outcomes of interest and met our inclusion criteria.

Harms Associated with the Duodenal-Jejunal Bypass Liner

We found two good- or fair-quality RCTs that met our inclusion criteria and reported data on DJBL-related AEs. In the first study, described above, 76.3% of DJBL patients had at least one AE, which consisted primarily of minor gastrointestinal complaints, abdominal pain, or discomfort (Koehestanie, 2014). The majority of these events occurred within the two weeks after implantation. Five (14.7%) events that were determined to be device-related required hospitalization. One patient had the device removed prematurely after it became blocked with food.

In a second fair quality RCT, described above, no serious AEs were reported (Schouten, 2010). However, 26 patients (100%) in the device group had at least one mild or moderate AE during follow-up. These events were most commonly nausea (76.9%) and upper abdominal pain (50%), primarily occurring during the first week after the procedure. Four (15.4%) patients had the device removed prior to the 12 or 24 weeks study period because of sleeve obstruction, dislocation or migration of the device, or epigastric pain. After migration occurred in one patient at four months post-implantation, safety concerns prompted researchers to remove the devices in four remaining patients who still had the device in situ. As such, only three (11.5%) patients kept the device for the full period of 24 weeks.

We found one additional case series that met our inclusion criteria and reported on harms. This study of 78 patients (84.4% female; mean age 50.8; mean BMI 43.8) reported that early removal occurred in 16 (20.5%) patients; 14 (18%) of these removals were due to complications such as device or anchor migration (De Moura, 2011).

Summary: Duodenal-Jejunal Bypass Liner

Key questions remain as to the efficacy and safety of the DJBL. Preliminary evidence suggests that there is low certainty that the DJBL has a comparable net health benefit or even a negative net health benefit for weight loss and comorbidity resolution relative to lifestyle interventions in patients with a BMI ≥35, and no evidence at all in patients at lower BMI levels. Given this level of certainty, and both published and manufacturer-reported data on potentially serious harms, we

judge the current evidence to be insufficient to draw firm conclusions on the DJBL's effects. Complications of the DJBL included device or anchor migration, epigastric pain, and sleeve obstruction; 2.9-20.5% of patients had the device removed prematurely across studies. An additional three RCTs were identified but are not discussed in this section due to poor quality and short duration of follow-up; characteristics of these studies can be found in Appendix Table B3. Also, as noted previously, enrollment in a large clinical trial of DJBL has been halted pending investigation of safety concerns.

Vagus Nerve Block *(Maestro® vBloc)*

We identified two good quality RCTs (Ikramuddin, 2014; Sarr, 2012) that examined the vagus nerve block device (vBloc). Detailed characteristics of these studies can be found in Appendix Table B1. There were no treatment-attributed deaths in either study.

Impact on Measures of Body Weight

Both RCTs of interest reported the percentage of EWL achieved by patients. In the first study, 239 patients (84% female; mean age 47; mean BMI 41) were randomized to receive the vBloc or sham device (Ikramuddin, 2014). After 12 months, vBloc recipients lost an average of 24.4% (95% CI: 20.8, 28.1) excess weight compared to 15.9% (95% CI: 11.9, 19.9) in the sham group (p=0.002 in post hoc testing). Thirty-eight percent of the vBloc group achieved at least 25% EWL, compared to 23% in the sham group (OR 2.0; 95% CI: 1.1, 3.8; p-value not reported).

In the second RCT, 294 patients (88% female; mean age 46; mean BMI 41) were implanted with the vBloc device and received either a complete block of vagal neural impulses or a very low, clinically unimportant level of charge (Sarr, 2012). In contrast to the first RCT, there were no statistical differences in the amount of EWL achieved between groups (17% vs. 16% for vBloc and low-charge, respectively). Correspondingly, the proportion of patients achieving 25% or more EWL did not statistically differ between groups (22-25%; p=NS).

Impact on Resolution of Comorbidities

We found no studies that reported resolution of comorbidities and met our inclusion criteria.

Outcomes in BMI <35

We found no studies that had a patient population with mean BMI <35 and met our inclusion criteria.

Impact on Other Outcomes

Sarr et al. (2012) measured QoL outcomes using both the IWQOL-Lite and SF-36 instruments. Scores on both improved for both groups between baseline and 12 months of follow-up; however, these improvements were not statistically different between groups (Sarr, 2012).

Harms Associated with the Vagus Nerve Block

We found two good-quality RCTs that reported data on AEs. The first RCT, described on page 53 reported that 3.7% (n=6; 95% CI: 1.4%, 7.9%; p<0.001) of recipients experienced a serious AE directly related to the device, implantation or revision, or therapy; an additional nine serious AEs were related to general intra-abdominal surgery (Ikramuddin, 2014). Serious AEs included neuroregulator malfunction requiring replacement (2), pain at the neuro-regulator site (1), atelectasis (1), emesis (1), and gallbladder disease (1). Five (3.1%) participants in the vBloc group and 8 (10.4%) in the sham group required removal of the device before 12 months.

The second RCT of interest, described on page 53 reported 35 serious AEs, 13 of which were related to the operative procedure (4), implantation or revision (5), or the device itself (4). Sixteen subjects (5.4%) required removal of the device before the trial's 12-month endpoint (eight for an AE, eight for subject decision), and 14 subjects (4.8%) required a revisionary procedure.

Summary: vBloc Device

We judge there to be low certainty of either a small or comparable net benefit for the vBloc device compared to a sham device in patients with a BMI ≥40, and the impact of the vBloc on comorbidities has not yet been determined. Given these results, and a not-inconsequential rate of device removal, we judge the evidence to be insufficient to draw firm conclusions on the benefits of the vBloc system in these patients. We found no evidence of the vBloc's effects in patients with BMI levels <40.

We identified two RCTs that examined the vBloc device. After 12 months follow-up in each study, vBloc patients lost 17-24.4% of excess body weight versus 15.9-16.0% EWL in control patients. The included studies did not report outcomes related to resolution or improvement in comorbidities. In both studies, 5.4% of patients had the device removed before study end; 3.4-4.4% of patients experienced serious complications related to the device, implantation, or revision.

4.3.3 Medications

Liraglutide *(Saxenda®)*

We identified a total of 15 reports of 11 good- or fair-quality RCTs that compared one or multiple doses of liraglutide to a placebo, orlistat (120 mg administered three times daily), or other anti-diabetic agent. Characteristics of included studies can be found in Appendix Tables B1-B2. Mean age ranged between 45.9 and 61 years (average across studies: 55.3), with no trial focusing exclusively on elderly or adolescent patients. Across studies, 34-82% of subjects were female (average: 49.7%) and mean BMI ranged from 24.9-41.1 (average: 32.7). Follow-up ranged from six months to two years (median: 6.5 months).

Nine trials focused solely on T2DM patients; eight of these studies provided additional anti-diabetic therapy to patients through metformin (1 g twice daily), rosiglitazone (4 mg twice daily), sulfonylureas (2-4 mg/day), or insulin. Two trials provided lifestyle counseling and prescribed a low calorie diet to all participants (Astrup, 2009; Lean, 2014; Wadden, 2013).

Impact on Measures of Body Weight

We identified five RCTs that compared liraglutide to a placebo. At a median of 26 weeks follow-up, liraglutide was associated with statistically significant but dose-dependent improvements in measures of weight change; patients who received lower doses of liraglutide (i.e., 0.6-0.9 mg) did not experience statistically significant weight change (Kaku, 2010; Marre, 2009).

Two studies reported outcomes at the recommended dose for obesity management (3 mg) (Astrup, 2009; Astrup 2012; Wadden, 2013). In a two-year crossover study, 564 participants (76% female; mean age 46; mean BMI 34.7) were randomly assigned to once-daily subcutaneous liraglutide (1.2, 1.8, 2.4 or 3.0 mg), placebo, or open-label orlistat (120 mg, three times daily). At the end of year one, all low-dose liraglutide and placebo recipients switched to liraglutide 2.4 mg, and eventually to 3.0 mg (between weeks 70-96) (Astrup, 2012). At 12 months follow-up, patients in the liraglutide 3 mg group lost 8% of total body weight, compared to 2.9% and 2.4% weight loss in the placebo and orlistat groups, respectively ($p<0.0001$ for both comparisons). In addition, 73% of patients taking liraglutide 3 mg lost more than 5% of total body weight compared to 28% in the placebo group and 44% in the orlistat group ($p<0.001$ for both comparisons). Results from the end of year two, which incorporated those patients who shifted from the placebo and lower-dose liraglutide groups into liraglutide 3 mg, maintain significantly better weight loss outcomes among liraglutide recipients relative to orlistat recipients (52% vs. 29% achieving more than 5% weight loss; $p<0.001$).

The other study was the SCALE Maintenance trial (Wadden, 2013). In this study, 422 patients (81.5% female; mean age 46.2; mean BMI 35.6) who lost at least 5% of total weight during a low-

calorie diet run-in were randomly assigned to liraglutide 3 mg or placebo for 56 weeks; both groups received in-person diet and exercise counseling during the duration of the trial. After 56 weeks, the liraglutide group had lost an average of 6% total body weight, and were 3.9 times more likely to achieve more than 5% weight loss (95% CI: 2.4, 6.1; p<0.001) relative to patients in the placebo group (Wadden, 2013).

The nine remaining studies compared lower doses of liraglutide to a placebo (Kaku, 2010; Zinman, 2009) and/or another anti-diabetic medication (de Wit, 2014; Garber, 2009; Lane, 2014; Marre, 2009; Mathieu, 2014; Nauck, 2009; Russell-Jones, 2009). Weight loss outcomes from these studies ranged from 0.2-5.3 kg; detailed results are summarized in Appendix B.

Impact on Resolution of Comorbidities

Improvement and/or resolution of comorbidities was reported in all 11 studies of interest. These studies reported important clinical measures related to T2DM, such as mean change in glycated hemoglobin, as well as the proportion of patients achieving the American Diabetes Association's (ADA) targeted levels of HbA1c <7% (Astrup, 2009; De Wit, 2014; Garber, 2009; Kaku, 2010; Lane, 2014; Marre, 2009; Mathieu, 2014; Nauck, 2009; Russell-Jones, 2009; Wadden, 2013; Zinman, 2009); one study reported changes in the proportion of individuals with metabolic syndrome (Astrup, 2009). The discussion below focuses on those studies reporting resolution in a binary fashion.

Astrup and colleagues found a beneficial effect of liraglutide 3.0 on T2DM indicators, finding 95.1% with normal glucose tolerance (defined as fasting plasma glucose <5.6 mmol/L or <7.8 mmol/L during oral glucose tolerance test) versus 65% in the placebo group (OR: 12.5; 95% CI: 2.9, 55; p<0.01) at 20 weeks follow-up. Similarly, metabolic syndrome improved more in patients taking standard-dose liraglutide than placebo; the proportion of patients with metabolic syndrome improved from baseline prevalence of 28% and 34%, in liraglutide and placebo groups, respectively to 11% and 21% at follow-up (significance not reported).

One additional study assessed the effects of lower doses of liraglutide monotherapy. Garber and colleagues randomized 746 patients (37.8% female; mean age 53; mean BMI 33) with T2DM to monotherapy with once daily liraglutide (1.2 or 1.8 mg) or the sulfonylurea derivative, glimepiride (8 mg) (Garber, 2009). After 52 weeks, a greater proportion of individuals achieved an HbA1c target of less than 7.0% with liraglutide 1.8 compared to glimepiride (50.9% vs. 27.8%; p<0.0001).
The eight remaining studies included in our review assessed the effects of lower doses of liraglutide (0.6-1.8 mg) in combination with one or more antidiabetic medications. The results of these studies are summarized in Appendix Tables B1-B2.

Retrospective Cohort Studies

We identified two fair-quality retrospective cohort studies. The first study evaluated weight loss and glycemic control outcomes in T2DM patients (% female not reported; mean age 51.5; mean BMI 42) who were treated with bariatric surgery (RYGB or VSG) or liraglutide (Cotugno, 2015). After 12 months, surgery patients lost more weight (38 kg vs. 5 kg; p<0.001), had a greater reduction in HbA1c (-2.2% vs. -1.3%; p<0.001), and had a greater proportion of patients who achieved ADA targeted levels of HbA1c (86% vs. 60%; p<0.03). The second study of interest compared 1,465 T2DM patients (47% female; mean age 56; BMI not reported) who filled prescriptions for either liraglutide or sitagliptin between January 2010 and December 2012 (Li, 2014). The study predicted liraglutide patients to have a greater reduction of HbA1c at 6-months follow-up than sitagliptin patients (0.95% points vs. 0.63% points; p<0.01) and to be more likely to reach the ADA's target HbA1c level of <7% (OR: 1.55; p<0.01).

Outcomes in BMI <35

Nine of the 11 liraglutide RCT patient populations had a mean baseline BMI <35. Given the variety of doses, follow-up duration, and combination therapies received by patients, it is not possible to conclude how the outcomes of these patients differed from those with higher BMIs (see Wadden, 2013 and Lane, 2014). Study characteristics and outcomes of all studies included in our review are summarized in Appendix B.

Impact on Other Outcomes

Three studies reported QoL-related outcomes (Bode, 2010; De Wit, 2014; Lean, 2014). Lean and colleagues stratified subscale outcomes of the IWQOL-Lite questionnaire (described previously) according to those who did and did not experience one or more episodes of nausea or vomiting (Lean, 2014). Scores improved across all subscales between baseline and follow-up with only marginal differences between those who experienced symptoms of nausea or vomiting.
In an analysis of patient-reported outcomes from the LEAD-3 trial (see Garber, 2009), Bode and colleagues assessed HRQoL using a series of scales: mental and emotional health, general health perceptions, composite HRQoL, composite cognitive function and performance, and analogue perceived health. Liraglutide (1.8 mg) groups had significantly better HRQoL at follow-up for mental and emotional health, psychological well-being, general positive effect, emotional ties, psychological stress and behavioral and emotional control, and general perceived health. A third study (De Wit, 2014) assessed diabetes-related distress using the Problem Areas in Diabetes Scale (PAID) instrument and found no change in QoL either within or between treatment groups.

Harms Associated with Liraglutide

We identified 13 RCTs that reported data on liraglutide-related AEs. The most commonly reported AEs were gastrointestinal disorders including nausea, vomiting, diarrhea, and constipation. These events occurred most frequently during the first four weeks of treatment. The rate of overall AEs ranged from 21-95.7% across studies, and discontinuation from AEs occurred in 0-15% of patients. These results are summarized in Appendix Table D3.

There were no serious AEs considered to be related to liraglutide. Acute pancreatitis occurred in 1-2 patients who were receiving varying doses of liraglutide in each of three studies (de Wit, 2014; Marre, 2009; Nauck, 2009).

Summary: Liraglutide

We judge there to be low certainty that dosing of liraglutide for weight loss provides a small net benefit vs. lifestyle interventions in patients with a BMI ≥30, due to modest levels of incremental weight loss and comorbidity resolution. Certainty was judged to be low because only two of the 11 available RCTs evaluated liraglutide at currently-labeled dosing for weight loss. It is also uncertain whether the benefits conferred from liraglutide can be sustained once treatment is discontinued or whether it can be safely taken for durations longer than one year. We found no evidence of liraglutide's benefits in patients with BMI levels <30.

The two studies with labeled dosing for weight loss (3 mg) found that patients lost 6-8% of total body weight after one year of follow-up and were more likely to have normal glucose tolerance relative to those in the placebo group. Changes in QoL were inconsistent across studies. The most commonly reported AEs were gastrointestinal disorders including nausea, vomiting, diarrhea, and constipation. Overall AE rates ranged from 21-95.7% across studies, and discontinuation due to AEs ranged from 0-15.0%.

Lorcaserin *(BELVIQ®)*

We identified a total of three good quality RCTs comparing one or multiple doses of lorcaserin to a placebo. Characteristics of included studies can be found in Appendix B. Mean age ranged between 43.8 and 52.7 (average across studies: 46.9); no trial exclusively examined elderly or adolescent patients. Across studies, 54.6-83.5% of patients were female (average: 72.6%), and mean BMI was 36.1 (range 36.0-36.2).

All studies compared lorcaserin (10 mg, administered once or twice daily) to a placebo and provided standardized nutritional and exercise counseling for all participants. Two of the three studies excluded patients with certain comorbidities, including hypertension and T2DM (Fidler, 2011;

Smith, 2010); the third study focused solely on patients with T2DM (O'Neil, 2012). All three studies had a follow-up duration of 52 weeks. No deaths occurred in any study.

Impact on Measures of Body Weight

Across all three RCTs of interest (Fidler, 2011; O'Neil, 2012; Smith, 2010), patients who took twice daily lorcaserin achieved greater weight loss than those receiving a placebo. Reductions in total body weight ranged from 4.5-5.8% among lorcaserin recipients, compared to a 1.5-2.8% mean decrease among those taking the placebo ($p<0.001$ for lorcaserin vs. placebo in all studies).

A significantly larger proportion of participants achieved 5% and 10% or more total weight loss with lorcaserin than with the placebo. Across studies, 44.1% (range 37.5%-47.5%) and 20.5% (range 16.3%-22.6%) of patients lost 5% and 10% or more total weight, respectively with lorcaserin, compared to 20.5% (range 16.1%-25%) and 7.3% (range 4.4%-9.7%) with a placebo.

Impact on Resolution of Comorbidities

As noted above, two of the three studies we reviewed excluded patients with certain comorbidities, including hypertension and T2DM (Fidler, 2011; Smith, 2010). The single remaining study (n=603; 55% female; mean age 52.7; mean BMI 36) focused on patients with T2DM who took metformin and/or a sulfonylurea for the duration of the trial (O'Neil, 2012). After 52 weeks 50.4% of the lorcaserin group and 26.3% of the placebo group achieved an HbA1c <7% ($p>0.001$) (O'Neil, 2012).

Outcomes in BMI <35

We found no studies that had an overall patient population with mean BMI <35; however, the BLOSSOM trial (n=4,004; 79.8% female; mean age 43.8; mean BMI 36.2) stratified weight loss outcomes by baseline BMI level (Fidler, 2011). Outcomes did not differ for patients in any BMI category for either the lorcaserin or placebo groups.

Impact on Other Outcomes

Three studies reported HRQoL outcomes using the IWQOL-Lite (Fidler, 2011; O'Neil 2012; Smith 2010). IWQOL-Lite scores improved in two studies in both the lorcaserin (+11.8 - +12.4) and placebo groups (+10.0 - +10.7; $p<0.001$ for both study comparisons) (Fidler, 2011; Smith 2010).

Harms Associated with Lorcaserin

We identified five good-quality RCTs that reported on harms. Across studies, headache, upper respiratory infection, nausea, and nasopharyngitis were the most commonly reported AEs. No study reported drug-related adverse effects of lorcaserin on laboratory measures, vital signs, or cardiac

valvulopathy. No deaths occurred in any study. Discontinuation of lorcaserin from drug-related adverse effects occurred in 4.3-8.6% of patients across studies. A single study reported that 82.6% of study participants experienced an AE (Fidler, 2011). These results are summarized in Appendix Table D4.

Summary: Lorcaserin

Using the ICER evidence rating matrix, we judge there to be moderate certainty of a small net benefit of lorcaserin (10 mg, administered once or twice daily) over lifestyle modification for weight loss in patients with BMI levels between 35-39.9. There is moderate certainty because while three good quality studies reported consistent weight-loss results, two studies excluded patients with common obesity-related comorbidities. We found no evidence of lorcaserin's benefits in populations with BMI levels ≤35 or ≥40.

In the three good-quality RCTs, reductions in total body weight were modest, ranging from 4.5-5.8% among lorcaserin recipients, compared to a 1.5-2.8% mean decrease among those taking the placebo ($p<0.001$ for lorcaserin vs. placebo in all studies). A single study reported outcomes related to comorbidity status and found 50.4% of lorcaserin patients versus 26.3% of placebo patients achieved an HbA1c <7% ($p>0.001$) (O'Neil, 2012). Discontinuation of lorcaserin from drug-related adverse effects occurred in 4.3-8.6% of patients across studies, and approximately 80% of study participants experienced any AE.

Naltrexone/Bupropion *(Contrave®)*

We identified a total of five good- or fair-quality RCTs comparing various doses of N/B combination therapy to a placebo; one study further included naltrexone monotherapy and bupropion monotherapy as active treatment groups (Greenway, 2009). Characteristics of included studies are reported in Appendix B. Mean age ranged between 43.2 and 53.9 (average across studies: 46.28); no study focused exclusively on elderly or adolescent patients. Four of the five trials were composed of over 84% females (average across five studies: 80.4%). The mean BMI ranged from 34.8-36.7 across studies (average: 36.1). Four of the five studies focused solely on patients with specific comorbidities, including dyslipidemia, hypertension, and T2DM (Apovian, 2013; Greenway, 2010; Hollander 2013; Wadden, 2011). Follow-up ranged from 48 to 56 weeks. All participants in all studies also received a lifestyle intervention, which included guidance on following a calorie-deficit diet, increasing physical activity, and modifying behavior.

Impact on Measures of Body Weight

We identified five good- or fair-quality RCTs that reported weight outcomes for N/B (Apovian, 2013; Greenway, 2009; Greenway, 2010; Hollander 2013; Wadden, 2011). Across four studies in which participants received standard doses of naltrexone (sustained release, 32 mg daily) combined with

bupropion (immediate release, 360 mg daily), patients lost 5-9.3% of total body weight after a median duration of follow-up of 56 weeks; patients who received a placebo lost 1.2-5.1% of total body weight ($p<0.05$ for all comparisons to N/B). A fifth fair-quality RCT (n=419; 88% female; mean age 43.2; mean BMI 34.8) combined naltrexone (sustained release, 32 mg daily) with a higher dose of bupropion (immediate release, 400 mg daily) and found that patients lost 5.4% of total body weight versus 0.8% in the placebo group ($p<0.05$) after 24 weeks (Greenway, 2009).

N/B was also associated with a significantly larger proportion of participants achieving 5% and 10% weight loss versus placebo. Across studies, 52.1% (range 44.5%-66.4%) and 27.7% (range 18.5%-41.5%) of patients who received N/B achieved 5% and 10% or more total weight loss, respectively, compared to 23.6% (range 16.0%-42.5%) and 9.7% (range 5.7%-20.2%) in the placebo groups ($p<0.05$ for all study comparisons).

Patients who participated in the COR-BMOD trial (n=793; 90.5% female; mean age 45.8; mean BMI 36.7) experienced better weight loss outcomes in both treatment and control groups than patients in other trials (Wadden, 2011). This difference may be the result of the COR-BMOD trial's more intensive group behavior modification program. Relative to patients in other trials, who lost on average 5.8% and 1.4% of total body weight in the N/B and placebo groups, respectively, N/B and placebo patients in the COR-BMOD trial lost 9.3% and 5.1%, respectively ($p<0.001$) (Wadden, 2011). There was also a higher proportion of patients achieving 5% and 10% weight loss in the COR-BMOD trial, with 66.4% and 41.5% achieving 5% and 10% or greater weight loss ($p<0.001$ for both comparisons) in the N/B group compared to an average of 48.5% and 24.2% across the other four studies.

Impact on Resolution of Comorbidities

A single RCT of 424 patients (53.6% female; mean age 53.9; mean BMI 36.5) reported outcomes related to improvement of comorbidities (Hollander, 2013). At week 56, 44.1% of N/B subjects achieved a target HbA1c <7% compared to 26.3% of placebo patients ($p<0.001$).

Outcomes in BMI <35

We identified a single study (n=419; 88% female; mean age 43.2; mean BMI 34.8) that had a patient population with a mean BMI <35 (Greenway, 2009). As noted above, patients received a higher dose of bupropion (immediate release, 400 mg daily) but did not achieve appreciably different outcomes from patients with slightly higher BMIs in other studies (Greenway, 2009). Of note, the average BMI across the other four N/B studies was 36.4, so it is unlikely that significant differences would be apparent.

Impact on Other Outcomes

Three studies reported HRQoL outcomes using the IWQOL-Lite. Across studies, overall weight-related QoL improved significantly more with N/B than with placebo, though both groups experienced an improvement. Between baseline and follow-up, patients taking standard dose N/B shifted from "moderate" to "mild" impairment with score improvements ranging from 10.9-13.4 points; by contrast, patients in the placebo groups improved their IWQOL-Lite scores by 6.4-10.3 points ($p<0.001$ for all comparisons with N/B) (Apovian, 2013; Greenway, 2010; Wadden, 2011).

An additional ongoing trial of the effectiveness of N/B in preventing MACE (major adverse cardiovascular events) in 9,000 obese patients was not included in our primary analysis set as results have not yet been published. However, interim results from the first 50% of study enrollees (Herper, 2015) indicate that N/B is not associated with reductions in the number of cardiovascular events such as myocardial infarction, stroke, or death from cardiovascular causes (102 placebo events vs. 90 N/B events; HR: 0.88; 95% CI: 0.66, 1.17).

Harms Associated with Naltrexone/Bupropion

We identified five good- or fair-quality studies that reported N/B-related AEs. Across studies, nausea, headache, and constipation were the most commonly reported treatment-emergent AEs. Nausea and other gastrointestinal symptoms occurred most frequently during dose escalation. There were no apparent drug-related negative effects of N/B on laboratory measures or electrocardiogram findings. Combination treatment was not associated with increased incidence of depression, suicidality, or other mood-related AEs. Discontinuation of N/B from adverse effects occurred in 4.3-29.3% of patients receiving standard-dose N/B across studies and 60.0-90.4% of patients experienced an AE. These results are summarized by study in Appendix Table D5.

Summary: Naltrexone/Bupropion

We judge there to be moderate certainty of a small net benefit associated with N/B over placebo, naltrexone monotherapy, or bupropion monotherapy with lifestyle intervention in patients with a BMI between 35 and 39.9. There is moderate certainty of benefit because although five good- or fair-quality studies showed consistent weight loss relative to comparator treatment, benefits were modest and more than half the patients in any individual study experienced a treatment-related AE. We also judge the evidence to be of low certainty for a small net benefit in patients with BMI 30-34.9 and T2DM based on the results of a single RCT in this population. Evidence was judged to be insufficient for all other BMI levels.

Across five available RCTs, participants who received standard doses of naltrexone (sustained release, 32 mg daily) combined with bupropion (immediate release, 360 mg daily) lost 5-7.8% of total body weight after a median duration of follow-up of 56 weeks; patients who received a

placebo lost 1.2-4.9% of total body weight. A single RCT reported outcomes related to improvement of comorbidities and found that 44.1% of patients taking N/B achieved a target HbA1c <7% compared to 26.3% of placebo patients (Hollander, 2013). Discontinuation of N/B from adverse effects occurred in 4.3-29.3% of patients receiving standard-dose N/B across studies, and 60.0-90.4% of patients experienced any AE.

Phentermine/Topiramate *(Qsymia®)*

We identified a total of eight good- or fair-quality reports of five RCTs; two reports were trial extensions, one of which maintained treatment and assignment, while the other changed the active treatment but maintained group assignment. Two reports were secondary analyses of previous RCTs.

All studies compared one or multiple doses of P/T extended release combination therapy to a placebo and/or phentermine or topiramate monotherapy. Characteristics of included studies can be found in Appendix B. Across studies, mean age ranged between 42.6 and 52.4 (average across studies: 48.1), 47-83% of patients were female (average: 69.6%), and mean BMI was 37.2 (range 35.4-42.2).

All studies provided a standardized lifestyle intervention for all participants; four of the five trials implemented the LEARN program (lifestyle, exercise, attitude, relationship, nutrition), which consisted of a calorie-deficit diet, increased water consumption, and increased physical activity. Three studies focused solely on patients with obesity-related comorbidities (Gadde, 2011; Garvey 2014a; Winslow, 2012). The median duration of follow-up was 28 weeks (range: 28-56).

Impact on Measures of Body Weight

Weight loss was assessed at various dose combinations of P/T in a total of five of the included studies. Across studies, P/T had a significant and dose-dependent effect on weight reduction. Two of the five trials prescribed phentermine (7.5 mg) plus topiramate (46 mg) at the recommended dose (Aronne 2013; Gadde 2011). In the CONQUER trial, 2,487 patients (70% female; mean age 51.1; mean BMI 36.5) with two or more obesity-related comorbidities were randomized to receive P/T (7.5/46 mg), P/T (15/92 mg), or placebo (Gadde, 2011). At 56 weeks follow-up, patients who received the recommended dose lost 7.8% of total body weight, compared to 9.8% and 1.2% in the 15/92 mg and placebo groups, respectively (P/T vs. placebo: $p<0.0001$). In a 56-week extension to the CONQUER trial, recipients of P/T (7.5/46 mg) lost 9.3% of total weight while placebo patients lost 1.8% ($p<0.001$) (Garvey, 2012). By study end, 75.2% of P/T (7.5/46 mg) patients had lost at least 5% of their initial body weight. Correspondingly, in a 28 week trial of 756 patients (79% female; mean age 44.7; mean BMI: 36.2), P/T (7.5/46 mg) recipients lost 8.46% of weight (versus 1.7%

weight loss in the placebo group; p<0.05), with 62.1% achieving 5% or more total weight loss (versus 15.5% in the placebo group; p<0.0001) (Aronne, 2013).

Aronne and colleagues also examined outcomes in patients who received higher doses of P/T (15/92 mg, once daily), as did three additional RCTs (Allison, 2012; Garvey 2014a; Winslow 2012). Despite a duration of follow-up that ranged from 28-56 weeks, these patients lost a similar amount of weight across studies: 9.2-10.9% of total body weight.

Impact on Resolution of Comorbidities

Five reports of three RCTs provided information on improvement in comorbidities. T2DM-related outcomes were described in three reports (Gadde, 2011; Garvey, 2014a; Garvey, 2014b). In a subgroup analysis of the CONQUER trial, Garvey and colleagues found a lower annualized incidence rate of T2DM among pre-diabetic patients who were assigned to either dose of P/T versus placebo, but this was significant only for the higher dose (1.8, 0.4, and 3.5 for the 7.5/46, 15/92, and placebo groups, respectively; 15/92 vs. placebo: p=0.0125) (Garvey, 2014b).

Another RCT of 130 patients (69% female; mean age 49.6; mean BMI 35.4) reported that a significantly greater percentage of P/T subjects achieved ADA-targeted HbA1c levels of <7.0% compared with placebo subjects (53% vs. 40%; p<0.05). In addition, 18.7% of P/T patients decreased the number of anti-diabetic medications taken during the 28-week study period versus 5.5% in the placebo group (significance not reported) (Garvey, 2014a).

A final RCT randomized 45 patients (47% female; mean age 52.4; mean BMI 35.7) with obstructive sleep apnea (OSA) to receive P/T (15/92 mg) or placebo (Winslow, 2012). By Week 28, the authors found significant improvements in OSA and related symptoms with P/T versus placebo: AHI (apnea-hypopnea index) decreased 31.5 points in P/T patients compared to a 16.6 point reduction in placebo patients (p=0.0084).

Outcomes in BMI <35

Although P/T is intended for patients with a BMI of 30 or greater (or 27+ with at least one obesity-related comorbidity), the mean baseline BMI of patients across studies ranged from 35-42. We therefore found no studies that had a patient population with mean BMI <35 and met our inclusion criteria.

Impact on Other Outcomes

We identified two studies that assessed changes in QoL. The CONQUER trial found greater improvements in most measurements of the IWQOL-Lite and SF-36 scales in both doses of P/T than with placebo (itemized data not reported) (Gadde, 2011). Alternatively, Winslow and colleagues did

not find significant differences between treatment groups (study characteristics described previously) in SF-36 QoL parameters, with the exception of the general health perceptions score, which favored the P/T 15/92 mg group (p=0.0103) (Winslow, 2012).

An additional three studies measured changes in depression symptoms using the PHQ-9 (Allison, 2012; Aronne, 2013; Gadde, 2011). Two studies found improvements in PHQ-9 scores among both treatment and placebo groups, but no significant differences emerged between groups (Allison, 2012; Aronne, 2013). A third study found that scores worsened slightly for all groups between baseline and follow-up but found no differences between groups (Gadde, 2011).

Harms Associated with Phentermine/Topiramate

We identified five good quality RCTs that reported P/T-related AEs. Across studies, dry mouth, dysgeusia, paraesthesia, insomnia, and constipation were among the most commonly reported treatment-emergent AEs. In a 56-week extension of the CONQUER trial, authors found that the incidence of AEs attributed to P/T declined over time, generally resolved on drug discontinuation, and occurred at a higher frequency with higher doses of treatment (Gadde, 2011; Garvey, 2012).

Discontinuation of the study drug due to AEs was most commonly attributed to insomnia, irritability, anxiety, headache, disturbance in attention, depression, dry mouth, and nephrolithiasis. Across studies, suicidality did not increase significantly, and psychiatric AEs such as depression and anxiety occurred primarily during the early phase of treatment. AEs occurred in 90.9-94.7% of patients, and 1.3-16.0% discontinued P/T due to treatment-emergent AEs. These results are summarized in Appendix Table D6.

Summary: Phentermine/Topiramate

We judge there to be moderate certainty of a small net benefit for P/T in improving weight loss relative to lifestyle modification and/or monotherapy of phentermine or topiramate in patients with BMI levels 35-39.9, and a low certainty of the same benefit in those with BMI ≥40. As with the other medications, certainty was low or moderate because of the modest levels of weight loss and comorbidity resolution observed, balanced against high rates of discontinuation due to AEs with this scheduled medication. We found no evidence on benefits in patients with BMI levels <35.

We identified a total of eight good- or fair-quality reports from five RCTs that compared phentermine/topiramate extended release (P/T) combination therapy to a placebo or to phentermine or topiramate monotherapy, all but one of which were conducted in patients with BMI levels between 35 and 39.9. In these trials, patients receiving the initial recommended dose combination (7.5/46 mg) lost 7.8-8.5% of total body weight (vs. 1-2% for placebo), while the range for those receiving the higher dose (15/92 mg) was 9.2-10.9%. Patients who received any dose of

P/T experienced greater improvement in obesity-related comorbidities such as T2DM, hypertension, and sleep apnea. We found no studies that had a patient population with mean BMI <35. Overall, 91-95% of patients experienced one or more AEs and 1.3-16.0% discontinued P/T due to AEs.

5. Model of Clinical and Economic Outcomes

ICER has adopted the following framework for assessing the comparative value of health care interventions, with value assessed according to two distinct constructs:

- *Care Value:*
    1. Comparative clinical effectiveness of each intervention vs. alternatives (considering both clinical benefits and harm)
    2. Any additional "non-clinical" benefits (e.g., reduced caregiver burden)
    3. Contextual considerations (no other acceptable treatment, vulnerable populations)
    4. Cost-effectiveness (incremental cost to achieve important patient outcomes vs. alternatives)

- *Health System Value:*
    1. Care value of the intervention of interest (as above) AND
    2. Potential effects of short-term budgetary impact from the intervention on other patients in the health care system

5.1 Prior Published Evidence on Costs and Cost-Effectiveness of Bariatric Surgery

As clinical evidence has accumulated on bariatric surgery over more than two decades, so too have data on the costs and potential cost-effectiveness of bariatric procedures in multiple populations. Below we summarize the findings of a comprehensive systematic review on the economic impact of bariatric surgery as well as those of several key studies made available after the publication of this systematic review.

Padwal et al. (2011)

Padwal and colleagues conducted a CADTH-sponsored systematic review of clinical evidence as well as information on costs and cost-effectiveness, based on available studies published through mid-January 2011 (Padwal, 2011). Economic studies were limited to those conducted for adult populations as well as to studies that adjusted estimates of survival for QoL (i.e., cost-utility studies). A total of 13 studies were evaluated, six of which were industry-sponsored. All evaluations involved comparisons of open or laparoscopic RYGB and/or LAGB, as well as usual or standard care. The primary focus of attention was on BMI levels of 35 or greater in all evaluations; in many of these, multiple BMI categories were tested.

Across all studies, bariatric procedures were shown to be cost-effective at willingness-to-pay thresholds <$50,000 per QALY gained over time horizons ranging from two years to lifetime. In

eight of 13 studies, cost-effectiveness estimates were below $15,000 per QALY gained. Higher cost-effectiveness ratios tended to be produced over shorter time horizons (i.e., 2-5 years). One study (Picot, 2009) showed an increase in two-year cost-effectiveness ratios with declining BMI (i.e., $35,904 per QALY gained at pre-operative BMI of 37, $115,230 per QALY gained for BMI of 34), but 20-year cost-effectiveness estimates were substantially lower ($3,000-$24,000 per QALY gained). Results were generally robust in sensitivity analyses, with reported probabilities of values <$50,000 per QALY gained ranging from 84-100%. One evaluation reported that LAGB was less costly and more effective than standard care on a lifetime basis, but only if diabetes remission lasted longer than 10 years (Keating, 2009); LAGB was no longer considered cost-effective when remission was less than two years in duration.

More recent economic evaluations focused on relevant US populations are summarized below.

Weiner et al., 2013

This was not a simulation model but a matched retrospective review of nearly 60,000 individuals enrolled at seven Blue Cross/Blue Shield health plans nationwide (Weiner, 2013). Patients were matched on an obesity-related propensity score that included BMI and obesity-related comorbidity data, as well as on age, sex, availability of prescription drug coverage, and plan location. An evaluation of regression-adjusted costs for each of the six years following surgery showed that mean annual costs increased significantly in the second and third years after surgery (by $500-$1,000) but then declined to pre-operative levels thereafter. By contrast, costs remained relatively stable in the nonsurgical group throughout follow-up. Importantly, mean annual costs of care were higher in the surgical group than in nonsurgical patients in each of the six years of the evaluation, particularly for inpatient services; the authors suggest that future studies should focus on the effects of bariatric surgery on overall health and well-being rather than its potential to produce a medical cost-offset.

Wang et al., 2014

Wang and colleagues developed a two-part simulation model to estimate the effects of bariatric procedures: a decision-analytic model focused on 1) the shorter-term (five-year) cost impact of surgery vs. standard care, and 2) a lifetime natural history model examining the possible trajectory of BMI change and its related effects beyond five years (Wang, 2014). Analyses were conducted for a 53 year-old female with a BMI of 44. On a lifetime basis, the cost-effectiveness of laparoscopic RYGB, open RYGB, and LAGB vs. standard care were estimated to be $6,600, $17,200, and $6,200 per QALY gained, respectively, based on available epidemiologic data on BMI change. Findings were similar when postsurgical BMI was assumed to remain stable. When patients were assumed to regain all weight by 15 years after surgery, cost-effectiveness estimates eroded somewhat but

remained well below $50,000 per QALY gained for laparoscopic RYGB and LAGB, and only slightly above for open RYGB ($59,500 per QALY gained).

Prior Published Evidence on Costs and Cost-Effectiveness of Other Obesity-Related Treatments

We did not find any prior publications addressing the costs and/or cost-effectiveness of the Maestro vBloc device or N/B therapy, the other treatment options of interest in this review.

ICER Simulation Model

To augment the available evidence on the economic impact of bariatric surgery and newer types of devices and medications, and to compare all procedures of interest in this evaluation, we developed our own decision-analytic model. The focus of attention in our model was on all four bariatric procedures of interest (i.e., RYGB, LAGB, VSG, and BPD±DS), as well as the newly-approved vBloc device, in comparison to standard nonsurgical management for all obese individuals (BMI ≥30) and in subgroups defined by BMI range (i.e., 30-34.9, 35-39.9, and ≥40). We also included data on the FDA-approved medication with the largest evidence base at an approved dose for obesity management, N/B.

5.2 Methods: Care Value

Type of Economic Evaluation

As in Wang et al. above (Wang, 2014), we developed a two-part model for this evaluation. We first conducted a cost-consequence analysis over a one-year time horizon to assess the immediate clinical and economic effects of bariatric surgery, a newer medication, and a newer type of device. For the bariatric surgery procedures, this analysis compared change in BMI, and proportions of patients with perioperative mortality, reoperation, and medical complications. For N/B sustained-release, we considered discontinuation due to AEs, while we included revision rates for the vBloc device. Costs of interest included those of treatment, reoperation, management of complications, and total costs. In addition, to explore the potential impact of obesity and its treatment on quantity and quality of life (QoL), a cost-utility analysis was also conducted over a ten-year time horizon based on assumed trajectories of BMI change after the various surgical, pharmacological, and device interventions. All analyses were conducted using Microsoft Excel 2010 (Microsoft Corporation, Seattle, Washington).

Target Population and Subgroups

The target population of the decision model included adults with obesity (BMI ≥30). We did not include children and adolescents in our modeling because of the paucity of comparative clinical evidence for each of the procedures of interest. We conducted an analysis for all patients with obesity (BMI ≥30) as well as for various classifications of obesity: moderately obese (BMI 30.0 – 34.9), severely obese (BMI 35.0 – 39.9), and morbidly obese (BMI ≥40).

Study Perspective

We adopted a public payer perspective for the reference case (i.e., primary analysis). In other words, costs were assumed to be those borne by the payer for services rendered. Patient out-of-pocket costs (e.g., copays, deductibles) were not considered. Indirect costs (e.g., lost work time, caregiver burden) were not included in the model.

Interventions

We evaluated the cost-effectiveness of the four types of bariatric surgery of focus in this evidence review, as well as the newer medication and type of device: RYGB, LAGB, VSG, and BPD±DS (i.e., with duodenal switch), N/B pharmacotherapy, and the vBloc device. These latter interventions were assessed as stand-alone treatment and in sequence with surgery reserved for treatment failures.

Comparator

The reference case analysis compared the various forms of bariatric surgery and newer types of devices and medications with conventional weight-loss treatments, including other prescription medication, dietary supplements, diet-control programs, exercise, psychotherapy, and nutritional counseling. Conventional treatments may have been delivered individually or in combination. We also conducted analyses comparing LAGB, VSG, and BPD±DS to RYGB as the most widespread form of bariatric surgery in the US.

Decision Modeling

The model was structured to incorporate the findings of RCTs that were included in the clinical review. The RCT outcomes were limited because of the short period of follow-up and use of surrogate outcomes such as BMI changes. Two main models were constructed: 1) a short-term model using RCT data related to change in BMI, complications and comorbidities at one year; and 2) a longer-term ten-year model that includes short-term outcomes from RCTs and incorporates estimates of QoL, mortality, and comorbid illness using observational study data over 10 years. For the long-term model, a Markov process was used to estimate costs and clinical outcomes in one-year cycles (see Figure 11 on page 72). The costs and effectiveness of each Markov cycle were

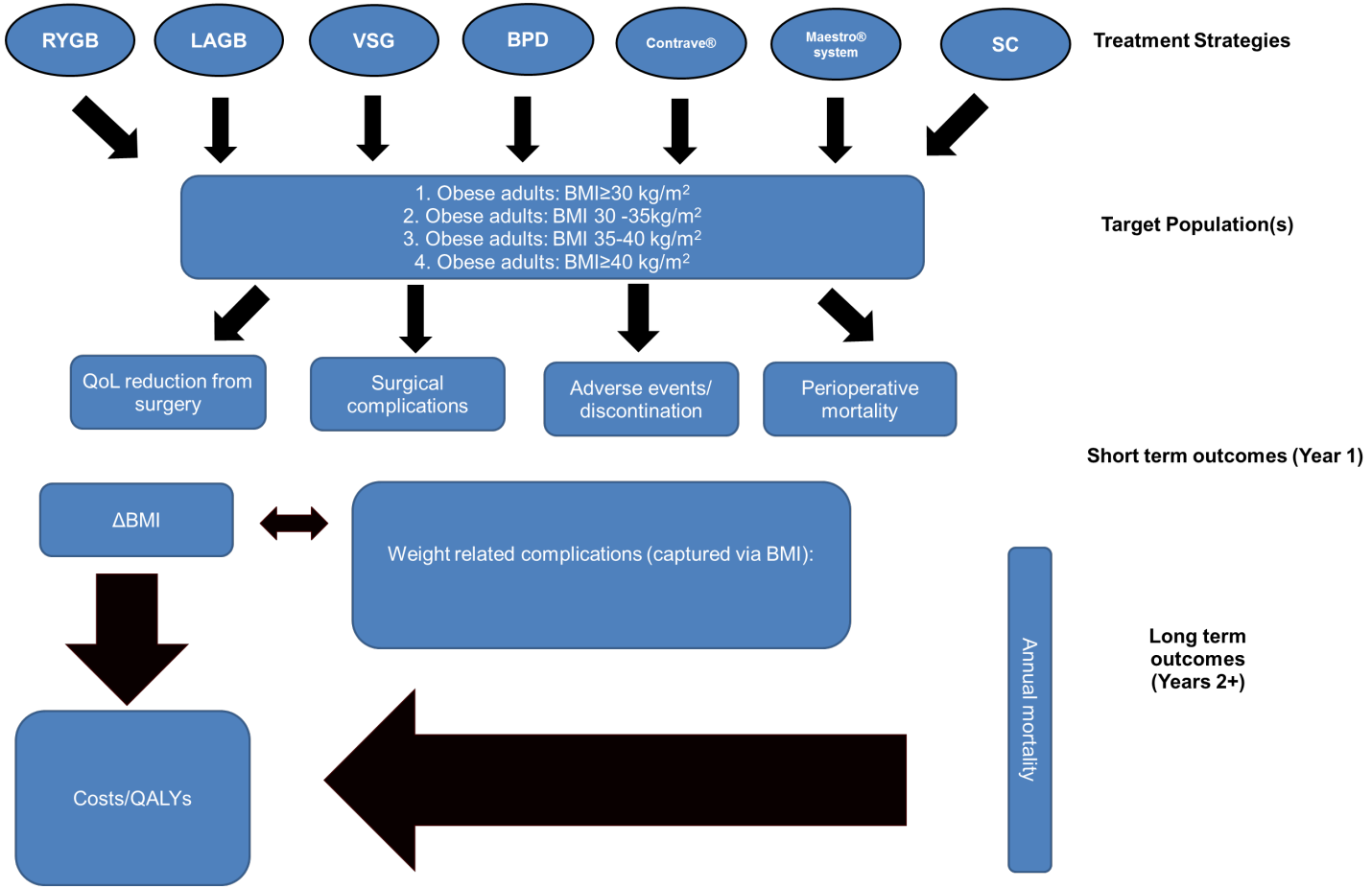
assigned based on the characteristics of survivors and equations relating these characteristics to costs and QoL (e.g., BMI, age of survivors).

The model outputs included QALYs, life-years gained, change in BMI, total health care costs, and incremental cost per QALY gained. Summary estimates of health care costs and QALYs were derived based on equations exploring their relationship with levels of BMI (as opposed to costs/QALYs being derived from individual obesity-related complications).

BMI

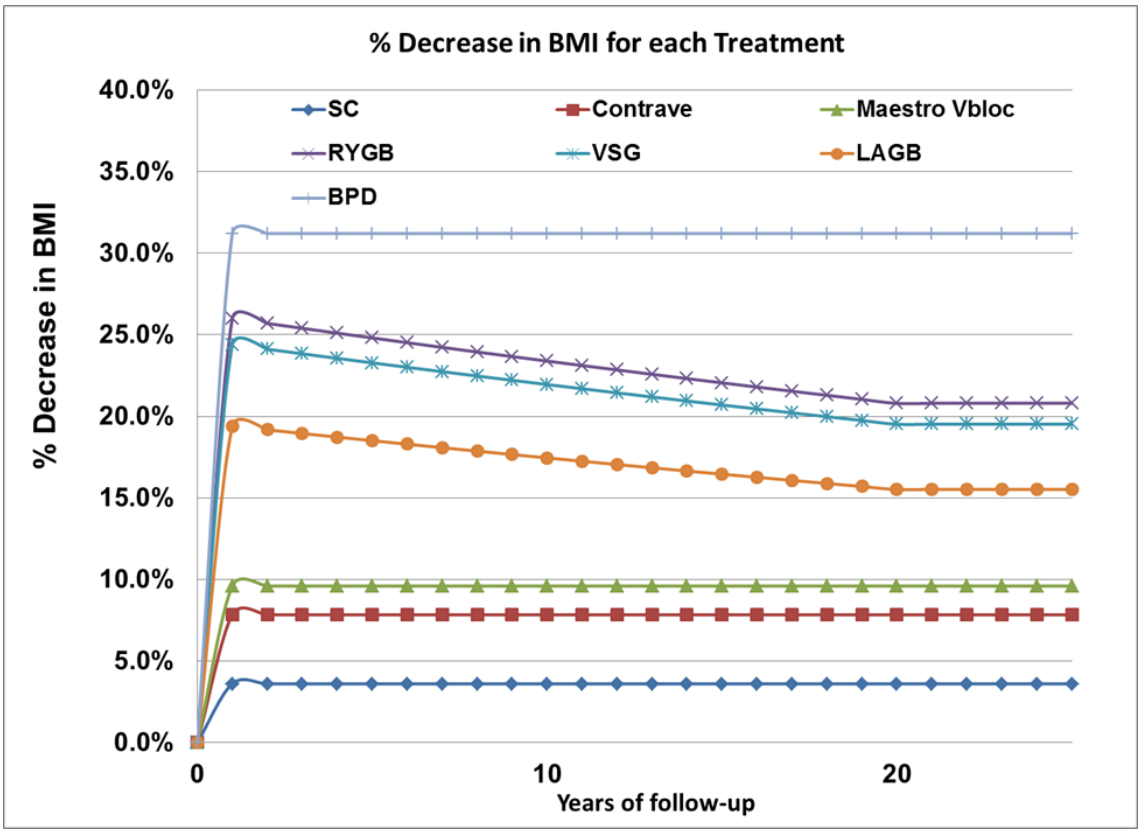
The initial BMI is based on the classification of obesity considered: all patients with obesity (BMI ≥30), moderately obese (BMI 30.0 – 34.9), severely obese (BMI 35.0 – 39.9), and morbidly obese (BMI ≥ 40). Patients with moderate obesity, severe obesity, and morbid obesity were assumed to have mean baseline BMIs of 32.5, 37.5 and 45, respectively, while all patients with BMI of 40 or greater were assumed to have a BMI of 40. The % change in BMI at one year between bariatric surgery strategies was based on the data derived from the evidence review. We used % change in BMI versus absolute change in BMI because the former translates better across the various obesity sub-populations considered in the model (Benoit, 2014). After one year, subsequent % changes in BMI in bariatric surgery were based on the results of observational studies. We assumed a 20% worsening in BMI change over 20 years for primarily restrictive procedures (RYGB, LAGB, VSG). For BPD, we assumed that the weight change is constant throughout, as the evidence suggests that primarily malabsorptive procedures may be better at sustaining weight loss (Dolan, 2004). In the absence of data, we assumed that values remained constant for N/B, vBloc, and standard care. Change in BMI is depicted graphically in Figure 12 on page 73.

Figure 11. Decision Model for Short- and Long-term Economic Outcomes of Bariatric Surgery



SC = standard care

Figure 12. Percentage Decrease in BMI by Duration of Follow-up for Treatment Strategies in Decision Model



Mortality

The risk of perioperative mortality among patients undergoing any of the bariatric procedures was 1.4%. The relative risk of perioperative mortality in patients receiving each type of bariatric surgery was based on mortality among participants who were identified in the clinical review as undergoing each of the procedures. The differences in short-term mortality by surgical approach were based on the calculated relative risk of mortality in the first year. RYGB, VSG, LAGB, and BPD±DS were assumed to be associated with relative risks of perioperative mortality of 0.47, 0.52, 0.58, and 1.09 respectively. We assumed no treatment-related mortality risk for N/B, vBloc, or standard care.

The risk of mortality among patients in subsequent years is based on age and BMI (see Appendix E). For standard care, N/B, and vBloc, we multiplied mortality rates in US Life Tables by BMI-specific mortality relative risks derived from the published literature (Campbell, 2010; Flegal, 2005). We assumed that bariatric surgery was associated with a reduction in the risk of mortality (RR 0.71; 95% CI 0.54, 0.92) in years 2+ for all bariatric surgeries versus standard care based on long-term data from the SOS study (Sjöström, 2013); given the controversy over this topic, we also conducted alternative analyses assuming no mortality benefit.

Quality of Life

Improvements in QoL are thought to be a key benefit of weight loss. We derived the estimates of BMI-specific utilities from a regression analysis of EuroQOL five dimensions questionnaire (EQ-5D) data from 2013 (Rothberg, 2014). In this study, the factors associated with change in HRQoL as assessed by the EQ-5D between baseline and six-month follow-up were baseline EQ-5D score, baseline BMI, baseline number of comorbidities, and change in BMI. The relationship among the various factors and HRQoL as assessed by EQ-5D were as follows:

$$\Delta \text{ EQ-5D} = 0.71995 - 0.68279 * \text{EQ-5D}_{Baseline} - 0.00285 * \text{BMI}_{Baseline} - 0.00957 * \text{NoComorb} + 0.0073 * \Delta \text{BMI}$$

Based on this, differential gains in HRQoL will be observed among the various BMI sub-populations considered. For example, patients with more severe obesity (i.e., BMI ≥40) will achieve greater gains in HRQoL than those with less severe obesity (i.e., BMI ≥30-34.9) given that patients with severe obesity (i.e., BMI ≥40) are more likely to have lower HRQoL at baseline, have more comorbidities, and achieve a greater reduction in weight. A detailed table of our estimates is in Appendix E.

Time Horizon

Various time horizons were considered. A one-year time frame focusing largely on clinical benefits and short-term complications was considered, as well a longer-term horizon of 10 years. We also considered five- and 25-year time horizons via sensitivity analysis.

Complications of Bariatric Surgery, N/B Pharmacotherapy, and the vBloc Device

The risk and relative risk of short-term complications was derived from the clinical review for each procedure of interest. The overall rate of reoperation was estimated to be 9.9%, to which relative risk estimates of 0.63, 0.32, 1.18, and 0.71 were applied for RYGB, VSG, LAGB, and BPD±DS, respectively. The rate of medically-managed complications was 11.8%; corresponding relative risk estimates by procedure were 0.93, 1.10, 0.14, and 1.76, respectively. We assumed 5.6% of patients who received the vBloc system would have the device removed by the end of year one due to complications. We assumed that 9.8% of patients using N/B therapy would discontinue due to AEs.

For participants undergoing bariatric surgery or subsequent surgery, it was assumed that the QoL was reduced by 0.21 (Campbell, 2010) for six weeks to account for surgery and recovery for all procedures except LAGB (a 4-week recovery was assumed). Medical complications were associated with a utility decrement of 0.11 (Campbell, 2010) over two weeks, while reoperations were associated with a decrement of 0.32 (Campbell, 2010) over four weeks. We made a simplifying assumption that all surgical complications would occur within the first year of the index surgery. We

conservatively assumed that N/B discontinuation and vBloc removal were not associated with a reduction in QoL, as treatment was assumed to stop immediately when AEs were experienced.

Estimating Resources and Costs

Direct costs for bariatric procedures were considered from the payer perspective; reimbursement rates from a public payer (the Washington State Health Care Authority [HCA]) were used based on data from a prior evidence review (Institute for Clinical and Economic Review, 2015) (see Table 6 below). Estimates of direct costs included professional and technical fees as well as facility charges for the bariatric surgery procedures. The cost of the vBloc system was assumed to be $17,500 based on the hospital list price supplied by the manufacturer (EnteroMedics, 2015b). Finally, the cost of N/B pharmacotherapy was assumed to be approximately $1,800 annually, based on the published wholesale acquisition cost (REDBOOK, 2015) less the mandated Medicaid price rebate (23.1%) for innovative medications (CMS, 2015).

Table 6. Costing Data for Health Economic Analysis

Cost Element	Total Costs	Source
Gastric bypass	$24,277	Washington HCA
Gastric banding	$17,483	Washington HCA
Biliopancreatic diversion (with or without duodenal switch)	$36,160	Washington HCA
Sleeve gastrectomy	$18,788	Survey of surgeons from state of Washington
Maestro® system	$17,500	Manufacturer
Naltrexone/bupropion sustained-release	$1,807*	REDBOOK, 2015
Medically managed complications	$5,625	Washington HCA
Surgically managed complications	$12,673	Washington HCA
Standard nonsurgical care	$3,746	Østbye 2014
Mortality	$41,503	Wang 2014
Annual costs – Obesity BMI (30-34.9)	$3,246	Østbye 2014
Annual costs – Obesity BMI (35-39.9)	$3,783	"
Annual costs – Obesity BMI (40+)	$4,028	"
% change in costs per BMI, Males **% change in costs per BMI, Females** **% change in costs per BMI, All**	3.93% 2.18% 2.97%	"

* 1,414 pills per year at $1.66 wholesale cost per pill (net of 23.1% Medi-Cal discount);

Health care costs for short-term surgical complications were also derived from the Washington HCA, while other costs at varying levels of BMI were derived from a recently published US study that reported costing data by BMI level for our population of interest (Østbye, 2014). We assumed that each unit of BMI decrease was associated with an approximate 3% decrease in health care expenditures.

Currency, Price Date, and Conversion

All costs are provided in 2014 US dollars.

Analytical Method

In addition to stratifying results by BMI, several univariate sensitivity and variability analyses were conducted to explore the effect of varying parameter values and assumptions within the model. These included the following factors of interest: time horizon, cost of bariatric procedure, mortality benefit for bariatric surgery, variation in BMI trajectory, and relationships between BMI and costs/QALYs.

We also conducted an analysis investigating the effect of treatment sequencing, in which we assumed patients using N/B or vBloc therapy who were unsuccessful with initial treatment would subsequently require RYGB surgery. In this analysis, 18% of patients using N/B are assumed to achieve "success" (10% or more total weight loss) and continue therapy, while 82% would switch to RYGB in year 2. For vBloc, 24% are assumed to achieve success (10% or greater total weight loss) and remain on vBloc, while 76% would switch to RYGB in year two.

We also effect separate sensitivity analyses varying the discontinuation/removal and success rates for N/B and vBloc between 50% and 200% of the base case estimate.

5.3 Results: Care Value

Reference Case Analysis – Costs and health consequences of bariatric surgery, N/B pharmacotherapy, vBloc, and nonsurgical standard care over one-year time frame

When compared with standard care in all patients with obesity (BMI≥30), the use of N/B, vBloc, RYGB, VSG, LAGB, and BPD±DS was associated with approximate decrements in BMI of 3.0, 3.8, 10.4, 9.8, 7.8, and 12.5 respectively (vs. 1.4 for standard care). Corresponding one-year costs were $5,355, $22,574, $30,099, $24,357, $22,035, and $42,979 respectively vs. $3,710 for standard care (see Table 7 on page 78). Mortality rates were similar among bariatric procedures but reoperation rates were lowest for VSG and highest for LAGB, while medical complication rates were highest for

VSG and BPD±DS. The rates of co-morbidity resolution were also similar among bariatric procedures but lowest for LAGB. Nearly 6% of vBloc patients had the device removed.

We also stratified results by BMI sub-categories; note that data on deaths, reoperations, and medical complications are not repeated in these stratified analyses since rates are identical to those in the overall population. Overall, the findings for BMI are more favorable for patients in the morbidly obese category (BMI ≥40) compared with those with lower BMI. For example, patients undergoing RYGB with a pre-operative BMI≥40 achieved larger absolute and % reductions in BMI (11.7, 29%) compared with those who had BMI 30-34.9 (8.45, 26%). The same trend occurred for other treatments, although the differences were less pronounced for N/B and vBloc given their more modest treatment effects. Total costs were similar across BMI categories for patients undergoing the four procedures but did increase in the standard care group as BMI increased, owing to the greater complexity of managing patients at higher levels of BMI.

Table 7. Costs and Consequences of Bariatric Surgery, N/B Pharmacotherapy, vBloc System, and Nonsurgical Standard Care over 1 year of Follow-up, among all Patients with BMI ≥30

Outcome/Cost	Standard Care	N/B	vBloc	RYGB	VSG	LAGB	BPD±DS
BMI ≥30							
Clinical Outcome							
BMI loss (mean)	1.4	3.0	3.8	10.4	9.8	7.8	12.5
Death (%)	1%	1%	1%	2%	2%	2%	2%
Reoperation (%)	0%	0%	6%**	6%	3%	12%	7%
Medical complication (%)	0%	0%	4%	11%	13%	2%	21%
Costs ($)							
Procedure	$0	$1,645	$17,500	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$0	$710	$787	$402	$1,478	$893
Other Complications*	$3,710	$3,710	$4,364	$5,035	$5,167	$4,570	$5,925
TOTAL	$3,710	$5,355	$22,574	$30,099	$24,357	$22,035	$42,979
BMI 30-34.9							
BMI loss (mean)	1.2	2.4	3.1	8.5	7.9	6.3	10.1
Total Cost ($)*	$3,042	$4,687	$21,813	$29,338	$23,596	$21,274	$42,218
BMI 35-39.9							
BMI loss (mean)	1.4	2.8	3.6	9.8	9.2	7.3	11.7
Total Cost ($)*	$3,500	$5,145	$22,384	$29,909	$24,167	$21,845	$42,789
BMI ≥40							
BMI loss (mean)	1.6	3.4	4.3	11.7	11.0	8.7	14.0
Total Cost ($)*	$4,269	$5,914	$23,359	$30,884	$25,142	$22,820	$43,764

NOTE: Because of rounding, performing calculations may not produce the exact results shown.

* Includes age-related background health care costs for obesity derived from Østbye 2014.

** 5.6% of vBloc patients assumed to have the device removed

Reference Case Analysis – *Cost-effectiveness of bariatric surgery, N/B sustained-release, Maestro® vBloc system and nonsurgical standard care over 10 year of follow-up, among all patients with BMI >30*

In the 10-year time horizon analysis, all active interventions of interest in this analysis, including surgery, device, and drug-based treatment, resulted in additional QALYs and increased costs compared with standard care (see Table 8 on page 80. The use of RYGB was associated with a gain of approximately 0.5 QALYs and incremental costs of nearly $20,000 ($54,110 vs. $34,923 for the standard care strategy). This led to an incremental cost per QALY of $37,423 for RYGB. VSG and LAGB are less costly but less effective than RYGB, while BPD±DS is more expensive and more

effective. The cost per QALY gained for BPD±DS was $77,574 in comparison to RYGB across all levels of BMI.

However, in comparison to standard care, cost-effectiveness estimates are similar for all surgery types (ranging from $29,000 - $47,000 per QALY gained). In contrast, the cost per QALY estimates for N/B therapy and the vBloc system relative to standard care were $131,250 and $109,543, respectively, owing to the more modest effects of these treatments on BMI.

In keeping with clinical results at one year of follow-up, cost-effectiveness values were most favorable in patients with a BMI ≥40. For example, RYGB produced 0.57 QALYs vs. standard care in these patients (vs. 0.41 in those with BMI 30-34.9) and was associated with incremental costs of approximately $18,000 (vs. $22,000 in less obese patients). As a result, the cost-effectiveness of RYGB in morbidly obese individuals was approximately $31,000 per QALY gained (vs. $53,000 in patients with BMI 30-34.9). Differences were similar for the more effective but more expensive BPD±DS procedure (cost-effectiveness ratios of ~$39,000 and ~$63,000 for BMI ≥40 and 30-34.9, respectively); differences were more pronounced for the less effective but less expensive N/B (~$123,000 and ~$173,000 respectively and vBloc therapies (~$102,000 and ~$143,000 respectively).

Table 8. Cost-effectiveness of Bariatric Procedures Over A 10-year Time Horizon, by Procedure and Preoperative BMI Level

BMI Level/Procedure	Cost ($)	Effectiveness (QALYs)	Cost-effectiveness ($/QALY gained)	
			Vs. SC	Vs. RYGB
BMI≥30				
Standard care	$34,923	7.5680	N/A	Less expensive & less effective
N/B	$47,732	7.6656	$131,250	Less expensive & less effective
vBloc	$51,471	7.7191	$109,543	Less expensive & less effective
RYGB	$54,110	8.0807	$37,423	N/A
VSG	$48,702	8.0417	$29,087	Less expensive & less effective
LAGB	$47,668	7.9252	$35,680	Less expensive & less effective
BPD±DS	$65,741	8.2307	$46,508	$77,574
BMI 30-34.9				
Standard care	$27,943	7.9418	N/A	Less expensive & less effective
N/B	$41,722	8.0213	$173,469	Less expensive & less effective
vBloc	$45,487	8.0645	$143,023	Less expensive & less effective
RYGB	$49,735	8.3529	$53,021	N/A
VSG	$44,298	8.3211	$43,122	Less expensive & less effective
LAGB	$42,738	8.2273	$51,826	Less expensive & less effective
BPD±DS	$61,410	8.4730	$63,011	$97,194
BMI 35-39.9				
Standard care	$32,538	7.6567	N/A	Less expensive & less effective
N/B	$46,184	7.7482	$149,212	Less expensive & less effective
vBloc	$49,994	7.7982	$123,392	Less expensive & less effective
RYGB	$52,886	8.1351	$42,534	N/A
VSG	$47,468	8.0986	$33,789	Less expensive & less effective
LAGB	$46,217	7.9898	$41,073	Less expensive & less effective
BPD±DS	$64,533	8.2751	$51,743	$83,224
BMI ≥40				
Standard care	$40,329	7.2846	N/A	Less expensive & less effective
N/B	$53,746	7.3939	$122,737	Less expensive & less effective
vBloc	$57,650	7.4540	$102,249	Less expensive & less effective
RYGB	$58,257	7.8630	$30,995	N/A
VSG	$53,047	7.8194	$23,784	Less expensive & less effective
LAGB	$52,255	7.6882	$29,552	Less expensive & less effective
BPD±DS	$69,329	8.0322	$38,790	$65,431

NOTE: Because of rounding, performing calculations may not produce the exact results shown.

Sensitivity Analyses – Bariatric Surgery vs. Standard Care

We performed a series of one-way sensitivity analyses on key model variables. A tornado diagram comparing RYGB with standard care using a 10-year time horizon for patients with BMI ≥30 is shown in Figure 13 on the following page. The incremental cost effectiveness rations (ICERs) range from $5,444 – $84,971/QALY. The model input having the greatest impact on incremental cost-effectiveness was time horizon. As the time horizon of the analysis is extended, the incremental cost per QALY gains for bariatric surgery estimates decrease. Similarly, as the time horizon of the analysis is reduced to as low as five years, the incremental cost per QALY gains for bariatric surgery increase (see Appendix E).

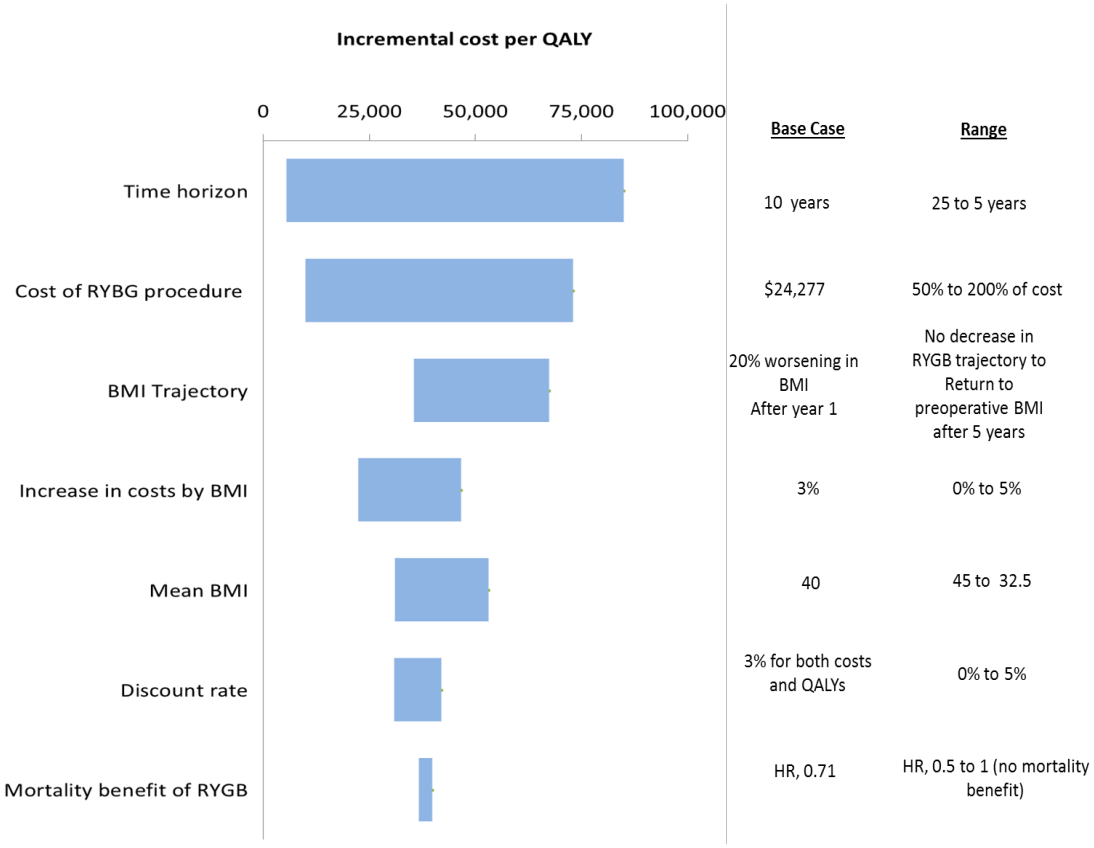
The model was also sensitive to the cost of bariatric surgery. In the base case, we assumed that the RYGB procedure costs were $24,277. However, in analyses varying this cost from 50% to 200% of the base case level, cost-effectiveness ratios ranged from $10,009 to $72,968 per QALY gained vs. standard care.

We also investigated a best case scenario in which we assumed that the BMI reduction observed in the first year is sustained over the time horizon as opposed to diminishing by 20%. Also considered was a worst case scenario of RYGB effectiveness, where we assumed that patients returned to preoperative BMI at 5 years post-surgery. The cost per QALY estimates for the 10-year time horizons did not materially differ from the base case analysis, ranging between $35,546 and $67,381 for RYGB compared with standard care under these scenarios.

We considered the impact of a varying all-cause mortality risk associated with bariatric surgery. If the base-case hazard ratio was reduced to 0.50 (versus 0.71) or increased to 1.0 (no mortality benefit), the ICER changed only slightly, to $36,651 and $39,756, respectively.

We also conducted a probabilistic sensitivity analysis on all relevant parameters. Results were similar to those of deterministic analyses and are summarized in Appendix E.

Figure 13. Tornado Diagram of Bariatric Surgery (RYGB) vs. Standard Care using 10 Year Time Horizon



Sensitivity analyses – Treatment Sequencing

Findings of our sensitivity analysis of treatment sequencing suggested somewhat improved cost-effectiveness ratios relative to the base case analysis. For example, continuation of N/B pharmacotherapy for patients achieving success but switching to RYGB surgery for those not successful would result in a cost per QALY gained of $44,196 vs. standard care, in comparison to a level of $131,250 in the base case. This was due to a number of factors, including a low assumed rate of success (18%), cessation of costs of drug therapy after failure, and ability to perform RYGB at a lower pre-operative BMI (due to the average effects of pharmacotherapy). By contrast, the cost-effectiveness of vBloc did not change appreciably in the sequencing scenario ($104,240 per QALY gained vs. $109,543 in the base case), as all patients would incur the cost of the device, eliminating most of the benefit of performing surgery at a lower BMI level.

We also conducted sensitivity analyses that varied the success rates of N/B and vBloc therapy from 50% to 200% of the base case levels. Cost-effectiveness of N/B therapy ranged from $40,856 to $52,834 per QALY gained, while vBloc estimates ranged from $95,233 to $128,595 per QALY

compared with standard care. Varying the drug discontinuation and device removal rates had similar effects.

5.4 Methods: Health-System Value

Given the emerging nature and/or pre-approval status of the devices and medications of interest in this review, we opted not to assess the potential health-system impact of their introduction to one or more populations of interest. Similarly, because the use of bariatric surgery is generally well-accepted in patients with BMI levels ≥35, we did not focus on the impact of surgery in these populations. Instead, we assessed the effect of allowing coverage of bariatric surgery in patients with a BMI between 30 and 34.9. Results were applied to all adults estimated to be currently enrolled in Medi-Cal, as well as the subset of these individuals estimated to have T2DM. An analysis of merged National Health and Nutrition Examination Survey (NHANES) and Medicaid Analytic eXtract (MAX) data indicate that the prevalence of BMI 30-34.9 in a Medicaid population is 27.7% (Dodd, 2013); a separate analysis of NHANES trend data indicates that the prevalence of diagnosed and undiagnosed diabetes in this BMI range is 11% (Gregg, 2004).

Findings were applied to a current estimate of Medi-Cal adult enrollees. Total enrollment (post-expansion) is currently estimated to be 11.7 million, of whom 56% are adults (~6.6 million) (California Healthline, 2014). We conservatively assumed that 25% of patients with BMI 30-34.9 (as well as among the subset with diabetes) would opt for surgery over standard treatment in any given year.

We calculated budget impact by taking the difference in year 1 costs from the care value analysis between VSG surgery and standard care; we chose VSG as the lowest-cost bariatric procedure still in widespread use (as noted previously, LAGB use has declined precipitously in the state). We also explored the effects if 10-year cost offsets were included, again based on data from the care value model. The overall PMPM Medi-Cal premium was estimated to be $552, based on data from Kaiser State Health Facts updated to 2014 levels (Kaiser State Health Facts, 2013; US Bureau of Labor Statistics, 2015).

5.5 Results: Health System Value

Findings from our health-system value analysis are presented in Table 9 on the following page. One year costs for standard obesity treatment are estimated to total $3,042 per patient, including costs of treatment and management of obesity-related complications. Offering VSG surgery would add $20,554 in costs over that of standard treatment, including the costs of surgery, complications, and ongoing patient management.

Of the 6.6 million adults currently enrolled in Medi-Cal, approximately 1.8 million are estimated to have a BMI in the range of 30-34.9. Replacing standard treatment with VSG surgery in 25% of these patients (~450,000) would increase one-year expenditures by approximately $9 billion, or approximately $66 PMPM, representing a 12% increase in the base PMPM of $552. Restricting availability of VSG to the subset of these patients with diabetes (~50,000) would increase expenditures by approximately $1 billion, or about $7 on a PMPM basis (1.3%).

We also adjusted cost differences for any offsets that would be realized from BMI improvements with surgery at 10 years. Data were again obtained from the care value analysis, and the difference in costs between VSG and standard care declines from $20,554 to $16,355 (a 20% cost offset). Under this scenario, use of VSG in 25% of Medi-Cal adults with BMI 30-34.9 would result in a PMPM impact of approximately $53 (9.6%), whereas use of VSG in 25% of those with a BMI of 30-34.9 and diabetes would increase expenditures by ~$6 PMPM (1.1%).

Table 9. Estimated Budgetary Impact of Use of Vertical Sleeve Gastrectomy among Medi-Cal Enrollees with BMI 30-34.9

Measure	All Enrollees (11.7 million)	Adults with BMI 30-34.9 (25% Receive Surgery)	Adults with BMI 30-34.9 and diabetes (25% receive surgery)
One-Year Costs*			
Total Expenditures	$77,500,800,000	$9,325,884,204	$1,025,847,262
PMPM	$552	$66.42	$7.31
% Increase	---	12.03%	1.32%
One-Year Costs with Offset **			
Total Expenditures	$77,500,800,000	$7,420,688,730	$816,275,760
PMPM	$552	$52.85	$5.81
% Increase	---	9.57%	1.05%

*Assumed one-year difference in cost between VSG and standard care of $20,554

**Adjusted one-year difference for downstream cost offsets of $16,355

5.6 Summary

Published evidence accumulated to date on care value suggests that bariatric surgery meets commonly-accepted thresholds for cost-effectiveness in comparison to standard care across multiple BMI categories, time horizons, and procedure types. By contrast, there are no currently published estimates of cost-effectiveness for newly-approved devices and drugs such as vBloc and Contrave®.

To better inform the comparisons of interest in our review, we developed a simulation model to compare the care value of four bariatric surgery procedures, the Maestro® vBloc system, and N/B sustained-release (Contrave®) to conventional weight-loss management for all obese individuals (BMI ≥30), as well as for subgroups defined by BMI range (i.e., 30-34.9, 35-39.9, and ≥40). Over the course of one year, across all levels of BMI and procedure type, we found that all interventions improved BMI levels but were subject to varying levels of complications and AEs, as well as increased overall costs. Over a 10-year timeframe, each intervention also resulted in improved quality-adjusted survival due primarily to the beneficial effects of lower weight on QoL. The more prominent weight loss from surgery also lowered obesity-related costs, offsetting the initial costs of surgery by as much as 30% over 10 years.

Cost-effectiveness estimates for bariatric surgery over 10 years ranged from approximately $24,000 to $63,000 per quality-adjusted life year (QALY) gained vs. conventional treatment, which is within commonly-accepted thresholds for cost-effectiveness (i.e., $50,000-$100,000 per QALY gained). These findings were robust to a range of sensitivity analyses, including elimination of mortality benefit for bariatric surgery and complete weight regain five years after surgery. Importantly, while the most favorable results were seen in patients with BMI ≥40 due to greater weight loss (and corresponding gains in QoL), surgery produces cost-effectiveness ratios within the commonly-accepted range among those with a BMI level of current policy interest (30-34.9), with findings ranging from $43,000 - $63,000 per QALY gained vs. conventional treatment.

In contrast, the much more modest weight loss achieved with the vBloc device and N/B pharmacotherapy, coupled with their high implantation and ongoing therapy costs, respectively, resulted in much higher cost-effectiveness ratios (>$100,000 per QALY vs. conventional treatment). Results were more favorable when these treatment options were considered “in sequence” with bariatric surgery for those failing initial treatment, in particular for a “drug first” regimen in which those with successful weight loss at one year continued to receive medication while patients requiring surgery were able to receive surgery after an initial weight loss.

Given the emerging nature of the evidence on devices and the modest benefits afforded by newer medications, we opted to focus our health-system value analysis on the use of bariatric surgery in patients with a BMI of 30-34.9. Under the assumption that 25% of adults currently enrolled in Medi-Cal would opt for vertical sleeve gastrectomy (the least expensive procedure in widespread use) over conventional weight-loss management, the one-year budgetary impact is substantial – $66, or a 12% increase over the current total PMPM Medi-Cal expenditure rate of $552. When availability is restricted to the subset of these patients who have diabetes, however, the budgetary impact declines to approximately $7 PMPM, or a 1.3% increase.

We note certain limitations of our analysis. First, the cost-effectiveness and budgetary impact of all of the interventions of interest are highly dependent on assumptions related to initial BMI loss and

forecasted change in BMI over any given time horizon. To address this limitation, we employed several BMI trajectory scenarios and found that results were robust under several assumptions. Second, there was considerable variation in patient populations, study design, and other features across studies, which limits the comparability of clinical evidence among interventions. As a result, we needed to make assumptions about the comparative clinical effects in the model. Rigorous, long-term studies are needed to better characterize the clinical benefits of drugs, devices, and surgical procedures for obesity, particularly in relation to durability of weight loss and comorbidity remission over the long term.

****

The California Technology Assessment Forum has previously reviewed:

- Bariatric Surgery for the Treatment of Type 2 Diabetes Mellitus, June 20, 2012
- Sleeve Gastrectomy as a Stand Alone Bariatric Procedure for Obesity, October 13, 2010
- Laparoscopic Adjustable Gastric Banding for Morbid Obesity, February 28, 2007
- Duodenal Switch for the Treatment of Morbid Obesity, February 11, 2004

This is the first CTAF review of all other interventions contained in this report.

References

Adams TD, Gress RE, Smith SC, et al. Long-Term Mortality after Gastric Bypass Surgery. *N Engl J Med*. 2007;357(8):753-761.

Abdel-Salam WN, Bekheit M, Katri K, Ezzat T, El Kayal ES. Efficacy of intragastric balloon in obese Egyptian patients and the value of extended liquid diet period in mounting the weight loss. *J Laparoendosc Adv Surg Tech A* 2013;23(3):220-224.

Alam ML, Van der Schueren BJ, Ahren B, et al. Gastric bypass surgery, but not caloric restriction, decreases dipeptidyl peptidase-4 activity in obese patients with type 2 diabetes. *Diabetes Obes Metab*. 2011;13:378-381.

Alami RS, Morton JM, Schuster R, et al. Is there a benefit to preoperative weight loss in gastric bypass patients? A prospective randomized trial. *Surg Obes Relat Dis*. 2007;3:141-145.

Albeladi B, Bourbao-Tournois C, Huten N. Short- and midterm results between laparoscopic roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy for the treatment of morbid obesity. *J Obes*. 2013;2013(January 2008).

Alfa Wali M, Ashrafian H, Schofield KL, et al. Is Social Deprivation Associated with Weight Loss Outcomes Following Bariatric Surgery? A 10-Year Single Institutional Experience. *Obes Surg*. 2014:2126-2132.

Alfredo G, Roberta M, Massimiliano C, Michele L, Nicola B, Adriano R. Long-term multiple intragastric balloon treatment - A new strategy to treat morbid obese patients refusing surgery: Prospective 6-year follow-up study. *Surg Obes Relat Dis*. 2014;10(2):307-311.

Alley JB, Fenton SJ, Harnisch MC, Tapper DN, Pfluke JM, Peterson RM. Quality of life after sleeve gastrectomy and adjustable gastric banding. *Surg Obes Relat Dis*. 2012;8(1):31-40.

Allison DB, Gadde KM, Garvey WT, et al. Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP). *Obesity*. 2012;20(2):330-342.

American Medical Association. AMA Adopts New Policies on Second Day of Voting at Annual Meeting. June, 2013. http://www.ama-assn.org/ama/pub/news/news/2013/2013-06-18-new-ama-policies-annual-meeting.page. Accessed May, 2015.

American Society for Metabolic and Bariatric Surgery. Estimate of bariatric surgery numbers. March, 2014. http://asmbs.org/resources/estimate-of-bariatric-surgery-numbers. Accessed September, 2014.

American Society for Metabolic and Bariatric Surgery. Story of Obesity Surgery. http://asmbs.org/resources/story-of-obesity-surgery. Accessed January, 2015.Andrew CG, Hanna W, Look D, McLean APH, Christou N V. Early results after laparoscopic Roux-en-Y gastric bypass: effect of the learning curve. *Can J Surg*. 2006;49(6):417-421.

Angrisani L, Cutolo PP, Formisano G, Nosso G, Vitolo G. Laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass: 10-year results of a prospective, randomized trial. *Surg Obes Relat Dis*. 2013;9(3):1-9.

Angrisani L, Lorenzo M, Borrelli V. Laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass: 5-year results of a prospective randomized trial. *Surg Obes Relat Dis*. 2007;3:127-132.

Angrisani L, Lorenzo M, Borrelli V, Giuffré M, Fonderico C, Capece G. Is bariatric surgery necessary after intragastric balloon treatment? *Obes Surg*. 2006;16(9):1135-1137.

Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity*. 2013;21(5):935-943.

Arena Pharmaceuticals/Eisai, Inc. BELVIQ for Chronic Weight Management. http://www.arenapharm.com/belviq. Accessed, May 2015.

Aronne LJ, Wadden T A, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity*. 2013;21(11):2163-2171.

Arterburn D, Powers JD, Toh S, et al. Comparative effectiveness of laparoscopic adjustable gastric banding vs laparoscopic gastric bypass. *JAMA Surg*. 2014;149(12):1279-1287.

Arterburn DE, Olsen MK, Smith V a, et al. Association Between Bariatric Surgery and Long-term Survival. 2015;313(1):62-70.

Astrup A, Carraro R, Harper A, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. 2012;(July 2011):843-854.

Astrup A, Rössner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009;374(9701):1606-1616.

Ballantyne GH, Farkas D, Laker S, Wasielewski a. Short-term changes in insulin resistance following weight loss surgery for morbid obesity: Laparoscopic adjustable gastric banding versus laparoscopic Roux-en-Y gastric bypass. *Obes Surg*. 2006;16:1189-1197.

Ballesta-Lopez C, Poves I, Cabrera M, Almeida JA, Macias G. Learning curve for laparoscopic Roux-en-Y gastric bypass with totally hand-sewn anastomosis: analysis of first 600 consecutive patients. *Surg Endosc*. 2005;19(4):519-24.

Basu, A. Forecasting distribution of body mass index in the United States: is there more room for growth? *Med Decis Making.* 2014;30(3): E1–E11.

Batsis J a, Lopez-Jimenez F, Collazo-Clavell ML, Clark MM, Somers VK, Sarr MG. Quality of life after bariatric surgery: a population-based cohort study. *Am J Med*. 2009;122(11):1055.e1-e1055.e10.

Bayham BE, Greenway FL, Bellanger DE, O'Neil CE. Early Resolution of Type 2 Diabetes Seen After Roux-en-Y Gastric Bypass and Vertical Sleeve Gastrectomy. *Diabetes Technol Ther*. 2012;14(1):30-34.

Becouarn G, Topart P, Ritz P. Weight loss prior to bariatric surgery is not a pre-requisite of excess weight loss outcomes in obese patients. *Obes Surg*. 2010;20:574-577.

Bekheit M, Katri K, Ashour MH, et al. Gender influence on long-term weight loss after three bariatric procedures: gastric banding is less effective in males in a retrospective analysis. *Surg Endosc*. 2014;28(8):2406-2011.

Belachew M, Legrand M, Vincent V, Lismonde M, Le Docte N, Deschamps V. Laparoscopic adjustable gastric banding. *World J Surg*. 1998;22(6):955-963.

Benaiges D, Flores-Le-Roux J a., Pedro-Botet J, et al. Impact of restrictive (Sleeve Gastrectomy) vs hybrid bariatric surgery (Roux-en-Y gastric bypass) on lipid profile. *Obes Surg*. 2012;22:1268-1275.

Benaiges D, Flores Le-Roux J a, Pedro-Botet J, et al. Sleeve gastrectomy and Roux-en-Y gastric bypass are equally effective in correcting insulin resistance. *Int J Surg*. 2013;11(4):309-313.

Benaiges D, Goday A, Ramon JM, Hernandez E, Pera M, Cano JF. Laparoscopic sleeve gastrectomy and laparoscopic gastric bypass are equally effective for reduction of cardiovascular risk in severely obese patients at one year of follow-up. *Surg Obes Relat Dis*. 2011;7(5):575-580.

Benamouzig R, Uzzan B, Airinei G, et al. Effects of Intragastric Balloon on Weight Loss, Physical Activity, Plasma Leptin and Ghrelin in Obese Patients, with Long-Term Follow-Up. *J Gastroenterol Hepatol Res*. 2013;2(8):744-749.

Benoit SC, Hunter TD, Francis DM, De La Cruz-Munoz N. Use of bariatric outcomes longitudinal database (BOLD) to study variability in patient success after bariatric surgery. *Obes Surg.* 2014;24(6), 936–43.

Biertho L, Steffen R, Ricklin T, et al. Laparoscopic gastric bypass versus laparoscopic adjustable gastric banding: A comparative study of 1,200 cases. *J Am Coll Surg*. 2003;197(03):536-547.

Birkmeyer NJO, Dimick JB, English WJ, et al. Hospital Complication Rates with Bariatric Surgery in Michigan. *JAMA*. 2010;304(4):435-442.

Black J a, White B, Viner RM, Simmons RK. Bariatric surgery for obese children and adolescents: a systematic review and meta-analysis. *Obes Rev*. 2013;14(4):634-644.

Bode BW, Testa M, Magwire M, et al. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(7):604-612.

Booth H, Khan O, Prevost T, et al. Incidence of type 2 diabetes after bariatric surgery: population-based matched cohort study. *LANCET Diabetes Endocrinol*. 2014;8587(14):1-6.

Bowne WB, Julliard K, Castro AE, Shah P, Morgenthal CB, Ferzli GS. Laparoscopic gastric bypass is superior to adjustable gastric band in super morbidly obese patients: A prospective, comparative analysis. *Arch Surg*. 2006;141(July 2006):683-689.

Boza C, Gamboa C, Awruch D, Perez G, Escalona A, Ibañez L. Laparoscopic Roux-en-Y gastric bypass versus laparoscopic adjustable gastric banding: Five years of follow-up. *Surg Obes Relat Dis*. 2010;6(5):470-475.

Boza C, Viscido G, Salinas J, Crovari F, Funke R, Perez G. Laparoscopic sleeve gastrectomy in obese adolescents: Results in 51 patients. *Surg Obes Relat Dis*. 2012;8(2):133-137.

Bozkurt S, Coskun H. The early results of intragastric balloon application of different BMI groups. *Eur Surg - Acta Chir AustriacA* 2012;44(6):383-387.

Brethauer S a., Kothari S, Sudan R, et al. Systematic review on reoperative bariatric surgery. American Society for Metabolic and Bariatric Surgery Revision Task Force. *Surg Obes Relat Dis*. 2014:1-21.

Brethauer S a, Harris JL, Kroh M, Schauer PR. Laparoscopic gastric plication for treatment of severe obesity. *Surg Obes Relat Dis*. 2012;7(November):15-22.

Breznikar B, Dinevski D. Bariatric surgery for morbid obesity: pre-operative assessment, surgical techniques and post-operative monitoring. *J Int Med Res*. 2009;37(5):1632-1645.

Brooks J, Srivastava ED, Mathus-Vliegen EMH. One-year adjustable intragastric balloons: Results in 73 consecutive patients in the UK. *Obes Surg*. 2014;24(5):813-819.

Brunault P, Jacobi D, Léger J, et al. Observations regarding "quality of life" and "comfort with food" after bariatric surgery: Comparison between laparoscopic adjustable gastric banding and sleeve gastrectomy. *Obes Surg*. 2011;21:1225-1231.

Bueter M, Thalheimer A, Lager C, Schowalter M, Illert B, Fein M. Who benefits from gastric banding? *Obes Surg*. 2007;17:1608-1613.

Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374(9683):39-47.

Busetto L, De Stefano F, Pigozzo S, Segato G, De Luca M, Favretti F. Long-term cardiovascular risk and coronary events in morbidly obese patients treated with laparoscopic gastric banding. *Surg Obes Relat Dis*. 2014;10(1):112-120.

Busetto L, Mirabelli D, Petroni ML, et al. Comparative long-term mortality after laparoscopic adjustable gastric banding versus nonsurgical controls. *Surg Obes Relat Dis*. 2007;3:496-502.

Busetto L, Segato G, De Luca M, et al. Preoperative weight loss by intragastric balloon in super-obese patients treated with laparoscopic gastric banding: A case-control study. *Obes Surg*. 2004;14(5):671-676.

California Healthline. Medi-Cal Enrollment Jumps to 11.3 Million. November 12, 2014. http://www.californiahealthline.org/capitol-desk/2014/11/medical-jumps-to-11-3-million. Accessed May, 2015.

Campbell J, McGarry L, Shikora SA, Hale BC, Lee JT, Weinstein MC. Cost-effectiveness of laparoscopic gastric banding and bypass for morbid obesity. *Am J Manag Care*. 2010;16(7): e174-187.

Campos GM, Rabl C, Roll GR, et al. Better weight loss, resolution of diabetes, and quality of life for laparoscopic gastric bypass vs banding: results of a 2-cohort pair-matched study. *Arch Surg*. 2011;146(2):149-155.

Carlin AM, O'Connor EA, Genaw JA, Kawar S. Preoperative weight loss is not a predictor of postoperative weight loss after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2008;4:481-485.

Carlin AM, Zeni TM, English WJ, et al. The comparative effectiveness of sleeve gastrectomy, gastric bypass, and adjustable gastric banding procedures for the treatment of morbid obesity. *Ann Surg*. 2013;257(5):791-797.

Chen C-Y, Lee W-J, Asakawa a, et al. Insulin secretion and interleukin-1β dependent mechanisms in human diabetes remission after metabolic surgery. *Curr Med Chem*. 2013;20:2374-2388.

Chen T, Godebu E, Horgan S, Mirheydar HS, Sur RL. The Effect of Restrictive Bariatric Surgery on Urolithiasis. *J Endourol*. 2012;27(2):242-4.

Chen W, Chang C-C, Chiu H-C, Shabbir A, Perng D-S, Huang C-K. Use of individual surgeon versus surgical team approach: surgical outcomes of laparoscopic Roux-en-Y gastric bypass in an Asian Medical Center. *Surg Obes Relat Dis*. 2012;8(2):214-219.

Chevallier J-M, Paita M, Rodde-Dunet M-H, et al. Predictive factors of outcome after gastric banding: a nationwide survey on the role of center activity and patients' behavior. *Ann Surg*. 2007;246(6):1034-1039.

Chevallier J-M, Zinzindohoué F, Douard R, et al. Complications after laparoscopic adjustable gastric banding for morbid obesity: experience with 1,000 patients over 7 years. *Obes Surg*. 2004;14:407-414.

Christ-Crain M, Stoeckli R, Ernst A, et al. Effect of gastric bypass and gastric banding on proneurotensin levels in morbidly obese patients. *J Clin Endocrinol Metab*. 2006;91(January):3544-3547.

Christou N, Efthimiou E. Five-year outcomes of laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass in a comprehensive bariatric surgery program in Canada. *Can J Surg*. 2009;52(6):E249-E258.

Cleveland Clinic. Procedures: Sleeve Gastrectomy. https://weightloss.clevelandclinic.org/sleevegastrectomy.aspx. Accessed January, 2015.

Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. *Cochrane database Syst Rev*. 2014;8(8):CD003641.

Compher CW, Hanlon A, Kang Y, Elkin L, Williams NN. Attendance at clinical visits predicts weight loss after gastric bypass surgery. *Obes Surg*. 2012;22:927-934.

Conason A. Substance Use Following Bariatric Weight Loss Surgery. *JAMA Surg*. 2013;148(2):145-50.

Cossu ML, Meloni GB, Alagna S, et al. Emergency surgical conditions after biliopancreatic diversion. *Obes Surg*. 2007;17:637-641.

Cottam DR, Atkinson J, Anderson A, Grace B, Fisher B. A case-controlled matched-pair cohort study of laparoscopic Roux-en-Y gastric bypass and Lap-Band?? patients in a single US center with three-year follow-up. *Obes Surg*. 2006;16:534-540.

Cotugno M, Nosso G, Saldalamacchia G, et al. Clinical efficacy of bariatric surgery versus liraglutide in patients with type 2 diabetes and severe obesity: a 12-month retrospective evaluation. *Acta Diabetol*. 2014;52(2):331-336.

Coupaye M, Breuil MC, Rivière P, et al. Serum vitamin D increases with weight loss in obese subjects 6 months after Roux-en-Y gastric bypass. *Obes Surg*. 2013;23:486-493.

Coupaye M, Puchaux K, Bogard C, et al. Nutritional consequences of adjustable gastric banding and gastric bypass: A 1-year prospective study. *Obes Surg*. 2009;19:56-65.

Courcoulas AP, Goodpaster BH, Eagleton JK, et al. Surgical vs Medical Treatments for Type 2 Diabetes Mellitus: A Randomized Clinical Trial. *JAMA Surg*. 2014;15213(7):707-715.

Courcoulas A, Schuchert M, Gatti G, et al. The relationship of surgeon and hospital volume to outcome after gastric bypass surgery in Pennsylvania: A 3-year summary. *Surgery*. 2003;134:613-623.

Cozacov Y, Roy M, Moon S, et al. Mid-term results of laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass in adolescent patients. *Obes Surg*. 2014;24(5):747-752.

Crea N, Pata G, Della Casa D, et al. Improvement of metabolic syndrome following intragastric balloon: 1 year follow-up analysis. *Obes Surg*. 2009;19(8):1084-1088.

Cutolo PP, Nosso G, Vitolo G, Brancato V, Capaldo B, Angrisani L. Clinical efficacy of laparoscopic sleeve gastrectomy vs laparoscopic gastric bypass in obese type 2 diabetic patients: A retrospective comparison. *Obes Surg*. 2012;22(2010):1535-1539.

Dallal RM, Quebbemann BB, Hunt LH, Braitman LE. Analysis of weight loss after bariatric surgery using mixed-effects linear modeling. *Obes Surg*. 2009;19:732-737.

Daskalakis M, Berdan Y, Theodoridou S, Weigand G, Weiner R a. Impact of surgeon experience and buttress material on postoperative complications after laparoscopic sleeve gastrectomy. *Surg Endosc Other Interv Tech*. 2011;25:88-97.

Dastis SN, François E, Deviere J, et al. Intragastric balloon for weight loss: Results in 100 individuals followed for at least 2.5 years. *Endoscopy*. 2009;41(7):575-580.

Davidson MH, Tonstad S, Oparil S, Schwiers M, Day WW, Bowden CH. Changes in cardiovascular risk associated with phentermine and topiramate extended-release in participants with comorbidities and a body mass index ≥27 kg/m2. *Am J Cardiol*. 2013;111(8):1131-1138.

De Castro ML, Morales MJ, Martínez-Olmos M a, et al. Safety and effectiveness of gastric balloons associated with hypocaloric diet for the treatment of obesity. *Rev Esp Enferm Dig*. 2013;105(9):529-536.

De Gordejuela AGR, Pujol Gebelli J, García NV, Alsina EF, Medayo LS, Masdevall Noguera C. Is sleeve gastrectomy as effective as gastric bypass for remission of type 2 diabetes in morbidly obese patients? *Surg Obes Relat Dis*. 2011;7(4):506-509.

De Jonge C, Rensen SS, Verdam FJ, et al. Endoscopic duodenal-jejunal bypass liner rapidly improves type 2 diabetes. *Obes Surg*. 2013;23(9):1354-1360.

Del Genio F, Alfonsi L, Marra M, et al. Metabolic and nutritional status changes after 10% weightloss in severely obese patients treated with laparoscopic surgery vs integrated medical treatment. *Obes Surg*. 2007;17:1592-1598.

De Moura EGH, Orso IRB, Martins BDC, et al. Improvement of insulin resistance and reduction of cardiovascular risk among obese patients with type 2 diabetes with the duodenojejunal bypass liner. *Obes Surg*. 2011;21(7):941-947.

De Wit HM, Vervoort GMM, Jansen HJ, De Grauw WJC, De Galan BE, Tack CJ. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: A 26 week, randomised clinical trial (ELEGANT). *DiabetologiA* 2014;57(9):1812-1819.

Deliopoulou K, Konsta A, Penna S, Papakostas P, Kotzampassi K. The impact of weight loss on depression status in obese individuals subjected to intragastric balloon treatment. *Obes Surg*. 2013;23(5):669-675.

Demaria EJ, Winegar D a, Pate VW, Hutcher NE, Ponce J, Pories WJ. Early postoperative outcomes of metabolic surgery to treat diabetes from sites participating in the ASMBS bariatric surgery

center of excellence program as reported in the Bariatric Outcomes Longitudinal Database. *Ann Surg*. 2010;252(3):559-566; discussion 566-567.

Deveney CW, MacCabee D, Marlink K, Welker K, Davis J, McConnell DB. Roux-en-Y divided gastric bypass results in the same weight loss as duodenal switch for morbid obesity. *Am J Surg*. 2004;187:655-659.

Dimick J, Nicholas LH, Ryan AM, Thumma JR, Birkmeyer JD. Bariatric surgery complications before vs after implementation of a national policy restricting coverage to centers of excellence. *JAMA*. 2013;309(8):792-799.

Dittmar M, Heintz a., Hardt J, Egle UT, Kahaly GJ. Metabolic and psychosocial effects of minimal invasive gastric banding for morbid obesity. *Metabolism*. 2003;52(12):1551-1557.

Dixon JB, Brien PEO, Playfair J, et al. Adjustable Gastric Banding and Conventional Therapy for Type 2 Diabetes. *JAMA*; 2008;299(3):316-323.

Dixon JB, Strauss BJG, Laurie C, O'Brien PE. Changes in body composition with weight loss: obese subjects randomized to surgical and medical programs. *Obesity (Silver Spring)*. 2007;15:1187-1198.

Dixon J, Mbbs P, Schachter L, et al. Surgical vs Conventional Therapy for Weight Loss Treatment of Obstructive Sleep Apnea: A Randomized Controlled Trial. *Jama*. 2012;308:1142-1149.

Doctors of Weight Loss. Laparoscopic Gastric Plication. 2015: http://doctorsofweightloss.com/gastric-plication. Accessed January, 2015.

Dolan K, Hatzifotis M, Newbury L, Fielding G. A Comparison of Laparoscopic Adjustable Gastric Banding and Biliopancreatic Diversion in Superobesity. *Obes Surg*. 2004;14(2):165-169.

Doldi SB, Micheletto G, Di Prisco F, Zappa M A, Lattuada E, Reitano M. Intragastric balloon in obese patients. *Obes Surg*. 2000;10(6):578-581.

Doldi SB, Micheletto G, Perrini MN, Librenti MC, Rella S. Treatment of morbid obesity with intragastric balloon in association with diet. *Obes Surg*. 2002;12(4):583-587.

Dorman RB, Rasmus NF, Al-Haddad BJS, et al. Benefits and complications of the duodenal switch/biliopancreatic diversion compared to the Roux-en-Y gastric bypass. *Surg (United States)*. 2012;152(4):758-767.

Ducarme G, Parisio L, Santulli P, Carbillon L, Mandelbrot L, Luton D. Neonatal outcomes in pregnancies after bariatric surgery: a retrospective multi-centric cohort study in three French referral centers. *J Matern Neonatal Med*. 2012;26(3):1-4.

Dumonceau JM, François E, Hittelet A, Mehdi AI, Barea M, Deviere J. Single vs repeated treatment with the intragastric balloon: A 5-year weight loss study. *Obes Surg*. 2010;20(6):692-697.

DuPree CE, Blair K, Steele SR, Martin MJ. Laparoscopic sleeve gastrectomy in patients with preexisting gastroesophageal reflux disease : a national analysis. *JAMA Surg*. 2014;149:328-334.

Edholm D, Svensson F, Näslund I, Karlsson FA, Rask E, Sundbom M. Long-term results 11 years after primary gastric bypass in 384 patients. *Surg Obes Relat Dis*. 2013;9(5):708-713.

El Chaar M, McDeavitt K, Richardson S, Gersin KS, Kuwada TS, Stefanidis D. Does patient compliance with preoperative bariatric office visits affect postoperative excess weight loss? *Surg Obes Relat Dis*. 2011;7(6):743-748.

Elakkary E, Elhorr A, Aziz F, Gazayerli MM, Silva YJ. Do support groups play a role in weight loss after laparoscopic adjustable gastric banding? *Obes Surg*. 2006;16(248):331-334.

Eldar SM, Heneghan HM, Brethauer S a., et al. Laparoscopic bariatric surgery for those with body mass index of 70-125 kg/m2. *Surg Obes Relat Dis*. 2012;8(6):736-740.

EnteroMedics, Inc. EnteroMedics announces FDA approval of vBloc® Vagal Blocking Therapy for the treatment of obesity. http://ir.enteromedics.com/releasedetail.cfm?ReleaseID=891316. January 14, 2015a. Accessed May, 2015.

EnteroMedics, Inc. 2015 Maestro device & patient kit hospital sale pricing. Supplied by manufacturer via email on April 30, 2015b.

Escalona A, Pimental F, Sharp A. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. *Ann Surg*. 2012;255(6):1080-1085.

Evans JD, Scott MH. Intragastric balloon in the treatment of patients with morbid obesity. *Br J Surg*. 2001;88(9):1245-1248.

Facchiano E, Iannelli A, Santulli P, Mandelbrot L, Msika S. Pregnancy after laparoscopic bariatric surgery: Comparative study of adjustable gastric banding and Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2012;8(4):429-433.

Faurschou A, Gyldenløve M, Rohde U, et al. Lack of effect of the glucagon-like peptide-1 receptor agonist liraglutide on psoriasis in glucose-tolerant patients - a randomized placebo-controlled trial. *J Eur Acad Dermatology Venereol*. 2015;29(3):555-559.

Fenske WK, Dubb S, Bueter M, et al. Effect of bariatric surgery-induced weight loss on renal and systemic inflammation and blood pressure: A 12-month prospective study. *Surg Obes Relat Dis*. 2013;9(4):559-568.

Fernandes M, Atallah AN, Soares BGO, et al. Intragastric balloon for obesity. *Cochrane Database Syst Rev*. 2007;(1).

Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: The BLOSSOM Trial. *J Clin Endocrinol Metab*. 2011;96(10):3067-3077.

Fierce Medical Devices. FDA puts hold on pivotal GI Dynamics trial for obesity device due to bacterial infection. March 6, 2015. http://www.fiercemedicaldevices.com/story/fda-puts-hold-pivotal-gi-dynamics-trial-obesity-device-due-bacterial-infect/2015-03-06. Accessed May, 2015.

Finkelstein E a., Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: Payer-and service-specific estimates. *Health Aff*. 2009;28.

Flegal K, Graubard B, Williamson D, Gail M. Excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2005;293(15):1861-1867.

Forlano R, Ippolito AM, Iacobellis A, et al. Effect of the BioEnterics intragastric balloon on weight, insulin resistance, and liver steatosis in obese patients. *Gastrointest Endosc*. 2010;71(6):927-933.

Fredheim JM, Rollheim J, Sandbu R, et al. Obstructive sleep apnea after weight loss: a clinical trial comparing gastric bypass and intensive lifestyle intervention. *J Clin Sleep Med*. 2013;9(5):427-432.

Fridman A, Moon R, Cozacov Y, et al. Procedure-related morbidity in bariatric surgery: A retrospective short- and mid-term follow-up of a single institution of the American College of Surgeons Bariatric Surgery Centers of Excellence. *J Am Coll Surg*. 2013;217(4):614-620.

Friedrich AE, Damms-Machado A, Meile T, et al. Laparoscopic sleeve gastrectomy compared to a multidisciplinary weight loss program for obesity--effects on body composition and protein status. *Obes Surg*. 2013;23:1957-1965.

Fujishima Y, Maeda N, Inoue K, et al. Efficacy of liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, on body weight, eating behavior, and glycemic control, in Japanese obese type 2 diabetes. *Cardiovasc Diabetol*. 2012;11(1):107.

Fuller NR, Pearson S, Lau NS, et al. An intragastric balloon in the treatment of obese individuals with metabolic syndrome: a randomized controlled study. *Obesity (Silver Spring)*. 2013;21(8):1561-1570.

Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): A randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9774):1341-1352.

Galvani C, Gorodner M, Moser F, et al. Laparoscopic adjustable gastric band versus laparoscopic Roux-en-Y gastric bypass: ends justify the means? *Surg Endosc*. 2006;20:934-941.

Gan SSH, Talbot ML, Jorgensen JO. Efficacy of surgery in the management of obesity-related type 2 diabetes mellitus. *ANZ J Surg*. 2007;77:958-962.

Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373(9662):473-481.

Garrido-Sanchez L, Murri M, Rivas-Becerra J, et al. Bypass of the duodenum improves insulin resistance much more rapidly than sleeve gastrectomy. *Surg Obes Relat Dis*. 2012;8(2):145-150.

Garvey WT. Ryan DH. Look M. Gadde KM. Allison DB. Peterson CA Schwiers M. Day WW. Bowden C. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine. *Am J Clin Nutr*. 2012;95(2):297-308.

Garvey WT, Ryan DH, Bohannon NJ V., et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. *Diabetes Care*. 2014a;37(12):3309-3316.

Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care*. 2014b;37(4):912-921.

Gehrer S, Kern B, Peters T, Christofiel-Courtin C, Peterli R. Fewer nutrient Deficiencies after laparoscopic sleeve gastrectomy (LSG) than after Laparoscopic Roux-Y-gastric bypass (LRYGB)-a prospective study. *Obes Surg*. 2010;20:447-453.

Genco A, Bruni T, Doldi SB, et al. BioEnterics intragastric balloon: The Italian experience with 2,515 patients. *Obes Surg*. 2005;15(8):1161-1164.

Genco A, Balducci S, Bacci V, et al. Intragastric balloon or diet alone? A retrospective evaluation. *Obes Surg*. 2008;18(8):989-992.

Genco A, Cipriano M, Bacci V, et al. Intragastric balloon followed by diet vs intragastric balloon followed by another balloon: A prospective study on 100 patients. *Obes Surg*. 2010;20(11):1496-1500.

Genco A, Cipriano M, Materia A, et al. Laparoscopic sleeve gastrectomy versus intragastric balloon: A case-control study. *Surg Endosc Other Interv Tech*. 2009;23(8):1849-1853.

Genco A, Lorenzo M, Baglio G, et al. Does the intragastric balloon have a predictive role in subsequent LAP-BAND® surgery? Italian multicenter study results at 5-year follow-up. *Surg Obes Relat Dis*. 2014;10(3):474-478.

Genco A, Maselli R, Frangella F, et al. Effect of consecutive intragastric balloon (BIB®) plus diet versus single BIB® plus diet on eating disorders not otherwise specified (EDNOS) in obese patients. *Obes Surg*. 2013;23(12):2075-2079.

Gersin KS, Rothstein RI, Rosenthal RJ, et al. Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. *Gastrointest Endosc*. 2010;71(6):976-982.

Giordano S, Victorzon M. The impact of preoperative weight loss before laparoscopic gastric bypass. *Obes Surg*. 2014;24(5):669-674.

Gonzalez R, Nelson LG, Murr MM. Does establishing a bariatric surgery fellowship training program influence operative outcomes? *Surg Endosc Other Interv Tech*. 2007;21:109-114.

Göthberg G, Gronowitz E, Flodmark C-E, et al. Laparoscopic Roux-en-Y gastric bypass in adolescents with morbid obesity--surgical aspects and clinical outcome. *Semin Pediatr Surg*. 2014;23(1):11-16.

Gould JC, Beverstein G, Reinhardt S, Garren MJ. Impact of routine and long-term follow-up on weight loss after laparoscopic gastric bypass. *Surg Obes Relat Dis*. 2007;3:627-630.

Gould JC, Kent KC, Wan Y, Rajamanickam V, Leverson G, Campos GM. Perioperative safety and volume: Outcomes relationships in bariatric surgery: A study of 32,000 patients. *J Am Coll Surg*. 2011;213(6):771-777.

Gracia-Solanas JA, Elia M, Aguilella V, et al. Metabolic syndrome after bariatric surgery. results depending on the technique performed. *Obes Surg*. 2011;21:179-185.

Gregg EW, Cadwell BL, Cheng YJ, et al. Trends in the prevalence and ratio of diagnosed to undiagnosed diabetes according to obesity levels in the US *Diabetes Care*. 2004;27(12):2806-2812.

Greenway FL, Dunayevich E, Tollefson G, et al. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. *J Clin Endocrinol Metab*. 2009;94(12):4898-4906.

Greenway FL, Fujioka K, Plodkowski R A, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595-605.

Halperin F, Ding S-A, Simonson DC, et al. Roux-en-Y Gastric Bypass Surgery or Lifestyle With Intensive Medical Management in Patients With Type 2 Diabetes: Feasibility and 1-Year Results of a Randomized Clinical Trial. *JAMA Surg*. 2014;02215.

Harder H, Nielsen L, Thi TDT, Astrup A The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. *Diabetes Care*. 2004;27(8):1915-1921.

Harnisch MC, Portenier DD, Pryor AD, Prince-Petersen R, Grant JP, DeMaria EJ. Preoperative weight gain does not predict failure of weight loss or co-morbidity resolution of laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Surg Obes Relat Dis*. 2008;4:445-450.

Hedberg J, Sundbom M. Superior weight loss and lower HbA1c 3 years after duodenal switch compared with Roux-en-Y gastric bypass - A randomized controlled trial. *Surg Obes Relat Dis*. 2012;8(3):338-343.

Helmiö M, Victorzon M, Ovaska J, et al. SLEEVEPASS: A randomized prospective multicenter study comparing laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity: preliminary results. *Surg Endosc*. 2012;26:2521-2526.

Herve J, Wahlen CH, Schaeken A, et al. What becomes of patients one year after the intragastric balloon has been removed? *Obes Surg*. 2005;15(6):864-870.

Himpens J, Dapri G, Cadière GB. A prospective randomized study between laparoscopic gastric banding and laparoscopic isolated sleeve gastrectomy: Results after 1 and 3 years. *Obes Surg*. 2006;16:1450-1456.

Hofsø D, Nordstrand N, Johnson LK, et al. Obesity-related cardiovascular risk factors after weight loss: A clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. *Eur J Endocrinol*. 2010;163:735-745.

Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type2 diabetes. *Diabetes Care*. 2013;36(12):4022-4029.

Horowitz M, Flint A, Jones KL, et al. Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2 diabetes. *Diabetes Res Clin Pract*. 2012;97(2):258-266.

Huang C-K, Lee Y-C, Hung C-M, Chen Y-S, Tai C-M. Laparoscopic Roux-en-Y gastric bypass for morbidly obese Chinese patients: learning curve, advocacy and complications. *Obes Surg*. 2008;18:776-781.

Huerta S, Dredar S, Hayden E, et al. Preoperative weight loss decreases the operative time of gastric bypass at a veterans administration hospital. *Obes Surg*. 2008;18:508-512.

Hutter MM, Schirmer BD, Jones DB, et al. First Report from the American College of Surgeons Bariatric Surgery Center Network. *Ann Surg*. 2011;254(3):410-422.

Iannelli A, Anty R, Schneck AS, Tran A, Hébuterne X, Gugenheim J. Evolution of low-grade systemic inflammation, insulin resistance, anthropometrics, resting energy expenditure and metabolic syndrome after bariatric surgery: a comparative study between gastric bypass and sleeve gastrectomy. *J Visc Surg*. 2013;150(4):269-275.

Iesari S, le Roux CW, De Gaetano A, Manco M, Nanni G, Mingrone G. Twenty-four hour energy expenditure and skeletal muscle gene expression changes after bariatric surgery. *J Clin Endocrinol Metab*. 2013;98(February 2013):E321-E327.

Ikramuddin S, Korner JK, Lee W, et al. Effect of reversible intermittent intra-abdominal vagal nerve blockade on morbid obesity: The ReCharge Randomized Clinical Trial. *JAMA*. 2014;312(9):915-922.

Ikramuddin S, Korner JK, Lee WJL, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes surgery Study Randomized Clinical Trial. *JAMA*. 2013;309(21):2240-2249.

Inabnet WB, Winegar D a., Sherif B, Sarr MG. Early outcomes of bariatric surgery in patients with metabolic syndrome: An analysis of the bariatric outcomes longitudinal database. *J Am Coll Surg*. 2012;214(4):550-556.

Iordens GIT, Klaassen RA, van Lieshout EMM, Cleffken BI, van der Harst E. How to train surgical residents to perform laparoscopic Roux-en-Y Gastric Bypass safely. *World J Surg*. 2012;36:2003-2010.

Jacques L, Syrek Jensen T, Schafer J, et al. *Proposed Decision Memorandum for CAG #00250R3 Reconsideration of Facility Certification Requirement for Coverage of Covered Bariatric Surger y Procedures*[Memorandum]. June 23, 2013: Centers for Medicare and Medicaid Services.

Jafari MD, Young MT, Smith BR, Phalen MJ, Nguyen NT. Volume and outcome relationship in bariatric surgery in the laparoscopic era. *Surg Endosc*. 2013;27:4539-4546.

Jamal MK, DeMaria EJ, Johnson JM, et al. Insurance-mandated preoperative dietary counseling does not improve outcome and increases dropout rates in patients considering gastric bypass surgery for morbid obesity. *Surg Obes Relat Dis*. 2006;2:122-127.

Jan JC, Hong D, Bardaro SJ, July L V., Patterson EJ. Comparative study between laparoscopic adjustable gastric banding and laparoscopic gastric bypass: single-institution, 5-year experience in bariatric surgery. *Surg Obes Relat Dis*. 2007;3:42-50.

Jenkins JT, Modak P, Galloway DJ. Prospective study of laparoscopic adjustable gastric banding in the west of Scotland. *Scott Med J*. 2006;51(1):37-41.

Jiménez A, Casamitjana R, Flores L, et al. Long-Term Effects of Sleeve Gastrectomy and Roux-en-Y Gastric Bypass Surgery on Type 2 Diabetes Mellitus in Morbidly Obese Subjects. *Ann Surg*. 2012;256(6):1.

Jiménez A, Ceriello A, Casamitjana R, Flores L, Viaplana-Masclans J, Vidal J. Remission of type 2 diabetes after Roux-en-Y gastric bypass or sleeve gastrectomy is associated with a distinct glycemic profile. *Ann Surg*. 2015;261(2):316-322.

Johnson LK, Andersen LF, Hofsø D, et al. Dietary changes in obese patients undergoing gastric bypass or lifestyle intervention: a clinical trial. *Br J Nutr*. 2012:1-8

Kaiser State Health Facts. 2013. http://kff.org/statedata/. Accessed May, 2015.

Kaku K, Rasmussen MF, Clauson P, Seino Y. Original Article. *Obe Metab*. 2010:341-347.

Kaleida Health. Bariatric Program: Weight Loss Surgery Options. http://www.kaleidahealth.org/Services/display.asp?pt=G&p=1301&s=690. Accessed January, 2015.

Karamanakos SN, Vagenas K, Kalfarentzos F, Alexandrides TK. Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: a prospective, double blind study. *Ann Surg*. 2008;247(3):401-407.

Karlsen TI, Lund RS, Røislien J, et al. Health related quality of life after gastric bypass or intensive lifestyle intervention: a controlled clinical study. *Health Qual Life Outcomes*. 2013;11:17.

Karmali S, Brar B, Shi X, Sharma AM, De Gara C, Birch DW. Weight recidivism post-bariatric surgery: A systematic review. *Obes Surg*. 2013;23:1922-1933.

Kashyap SR, Bhatt DL, Wolski K, et al. Metabolic Effects of Bariatric Surgery. *Diabetes care*. 2013;36(8):2175-2182.

Keating CL, Dixon JB, Moodie ML, et al. cost-effectiveness of surgically induced weight loss for the management of Type 2 diabetes: Modeled lifetime analysis. *Diabetes Care*. 2009;32(4):567-74.

Kehagias I, Karamanakos SN, Argentou M, Kalfarentzos F. Randomized Clinical Trial of Laparoscopic Roux-en-Y Gastric Bypass Versus Laparoscopic Sleeve Gastrectomy for the Management of Patients with BMI < 50 kg/m2. *Obes Surg*. 2011;21:1650-1656.

Keidar A, Hershkop KJ, Marko L, et al. Roux-en-Y gastric bypass vs sleeve gastrectomy for obese patients with type 2 diabetes: A randomised trial. *Diabetologia*. 2013;56:1914-1918.

Khoo CM, Chen J, Pamuklar Z, Torquati A. Effects of Roux-en-Y gastric bypass or diabetes support and education on insulin sensitivity and insulin secretion in morbidly obese patients with type 2 diabetes. *Ann Surg*. 2014;259(3):494-501.

Kim SH, Abbasi F, Lamendola C, Liu A, Reaven G. Bene fi ts of Liraglutide Treatment in Overweight and Obese Older Individuals With Prediabetes. *Diabetes Care*. 2013;36:3276-3282.

Kim TH, Daud A, Ude AO, et al. Early US outcomes of laparoscopic gastric bypass versus laparoscopic adjustable silicone gastric banding for morbid obesity. *Surg Endosc*. 2006;20:202-209.

Koehestanie P, de Jonge C, Berends FJ, Janssen IM, Bouvy ND, Greve JWM. The Effect of the Endoscopic Duodenal-Jejunal Bypass Liner on Obesity and Type 2 Diabetes Mellitus, a Multicenter Randomized Controlled Trial. *Ann Surg*. 2014;00(00):1-9.

Kokkinos A, Alexiadou K, Liaskos C, et al. Improvement in cardiovascular indices after Roux-en-Y gastric bypass or sleeve gastrectomy for morbid obesity. *Obes Surg*. 2013;23:31-38.

Konopko-Zubrzycka M, Baniukiewicz A, Wróblewski E, et al. The effect of intragastric balloon on plasma ghrelin, leptin, and adiponectin levels in patients with morbid obesity. *J Clin Endocrinol Metab*. 2009;94(5):1644-1649.

Korner J, Inabnet W, Febres G, et al. Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass. *Int J Obes (Lond)*. 2009;33(7):786-795.

Kotzampassi K, Grosomanidis V, Papakostas P, Penna S, Eleftheriadis E. 500 Intragastric balloons: What happens 5 years thereafter? *Obes Surg*. 2012;22(6):896-903.

Kruger RS, Pricolo VE, Streeter TT, Colacchio D a., Andrade U a. A bariatric surgery center of excellence: Operative trends and long-term outcomes. *J Am Coll Surg*. 2014;218(6):1163-1174.

Laferrère B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2008;93(January):2479-2485.

Lane W, Weinrib S, Rappaport J, Hale C. The effect of addition of liraglutide to high-dose intensive insulin therapy: a randomized prospective trial. *Diabetes Obes Metab*. 2014;16(9):827-832.

Leahey TM, Bond DS, Irwin SR, Crowther JH, Wing RR. When is the best time to deliver behavioral intervention to bariatric surgery patients: before or after surgery? *Surg Obes Relat Dis*. 2009;5(1):99-102.

Lean M, Carraro R, Finer N, et al. Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. *Int J Obes*. 2014;38(5):689-697.

Lee DY, Guend H, Park K, et al. Outcomes of laparoscopic Roux-en-Y gastric bypass versus laparoscopic adjustable gastric banding in adolescents. *Obes Surg*. 2012;22:1859-1864.

Lee H, Kim D, Lee S, Nam K, Kim E. Initial evaluation of Laparoscopic Roux-en-Y gastric bypass and adjustable gastric banding in Korea: A single institution study. *Obes Surg*. 2010;20:1096-1101.

Lee Y-M, Low HC, Lim LG, et al. Intragastric balloon significantly improves nonalcoholic fatty liver disease activity score in obese patients with nonalcoholic steatohepatitis: a pilot study. *Gastrointest Endosc*. 2012;76(4):756-760.

Leeman MF, Ward C, Duxbury M, De Beaux A C, Tulloh B. The intra-gastric balloon for pre-operative weight loss in bariatric surgery: Is it worthwhile? *Obes Surg*. 2013;23(8):1262-1265.

Lennerz BS, Wabitsch M, Lippert H, et al. Bariatric surgery in adolescents and young adults—safety and effectiveness in a cohort of 345 patients. *Int J Obes (Lond)*. 2014;38(3):334-340.

Leonetti F, Capoccia D, Coccia F, et al. Obesity, type 2 diabetes mellitus, and other comorbidities: A prospsective cohort study of laparoscopic sleeve gastrectomy vs medical treatment. Arch Surg. 2012; 147(8): 694-700.

Leslie DB, Dorman RB, Serrot FJ, et al. Efficacy of the Roux-en-Y gastric bypass compared to medically managed controls in meeting the american diabetes association composite end point goals for management of type 2 diabetes mellitus. *Obes Surg*. 2012;22:367-374.

Leyba JL, Aulestia SN, Llopis SN. Laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy for the treatment of morbid obesity. a prospective study of 117 patients. *Obes Surg*. 2011;21:212-216.

Li C, Li J, Zhang Q, et al. Efficacy and safety comparison between liraglutide as add-on therapy to insulin and insulin dose-increase in Chinese subjects with poorly controlled type 2 diabetes and abdominal obesity. *Cardiovasc Diabetol*. 2012;11(1):142.

Li Q, Chitnis A, Hammer M, Langer J. Real-World Clinical and Economic Outcomes of Liraglutide Versus Sitagliptin in Patients with Type 2 Diabetes Mellitus in the United States. *Diabetes Ther*. 2014;5(2):579-590.

Li VK, Pulido N, Martinez-Suartez P, et al. Symptomatic gallstones after sleeve gastrectomy. *Surg Endosc*. 2009;23:2488-2492.

Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: A randomized controlled trial. *Diabetes Res Clin Pract*. 2013;101(1):50-56.

Lier H, Biringer E, Stubhaug B, Eriksen HR, Tangen T. Psychiatric disorders and participation in Pre- and postoperative counselling groups in bariatric surgery patients. *Obes Surg*. 2011;21:730-737.

Lier H, Biringer E, Stubhaug B, Tangen T. The impact of preoperative counseling on postoperative treatment adherence in bariatric surgery patients: A randomized controlled trial. *Patient Educ Couns*. 2012;87(3):336-342.

Lim DM, Taller J, Bertucci W, Riffenburgh RH, O'Leary J, Wisbach G. Comparison of Laparoscopic Sleeve Gastrectomy to Laparoscopic Roux-en-Y Gastric Bypass for Morbid Obesity in a Military Institution. *Surg Obes Relat Dis*. 2014;10(2):269-276.

Lindsey ML, Patterson WL, Gesten FC, Roohan PJ. Bariatric surgery for obesity: Surgical approach and variation in in-hospital complications in New York State. *Obes Surg*. 2009;19:688-700.

Lips MA., De Groot GH, De Kam M, et al. Autonomic nervous system activity in diabetic and healthy obese female subjects and the effect of distinct weight loss strategies. *Eur J Endocrinol*. 2013;169:383-390.

Lips MA, De Groot GH, Van Klinken JB, et al. Calorie restriction is a major determinant of the short-term metabolic effects of gastric bypass surgery in obese type 2 diabetic patients. *Clin Endocrinol (Oxf)*. 2014;80:834-842.

Livingston EH. Bariatric Surgery Outcomes at Designated Centers of Excellence vs Nondesignated Programs. Arch Surg. 2009;144(4):319-325.

Livingston EH, Burchell I. Reduced access to care resulting from centers of excellence initiatives in bariatric surgery. *Arch Surg*. 2010;145(10):993-997.

Livingston EH, Elliot AC, Hynan LS, Engel E. When Policy Meets Statistics: The Very Real Effect that Questionable Statistical Analysis has on Limiting Health Care Access for Bariatric Surgery. *Arch Surg*. 2007;*142*(10): 979–987.

Loffredo A, Cappuccio M, De Luca M, et al. Three years experience with the new intragastric balloon, and a preoperative test for success with restrictive surgery. *Obes Surg*. 2001;11(3):330-333.

Lutfi R, Torquati A, Sekhar N, Richards WO. Predictors of success after laparoscopic gastric bypass: a multivariate analysis of socioeconomic factors. *Surg Endosc*. 2006;20:864-867.

Ma Y, Pagoto SL, Olendzki BC, et al. Predictors of weight status following laparoscopic gastric bypass. *Obes Surg*. 2006;16:1227-1231.

Maciejewski ML, Livingston EH, Smith V a, et al. Survival among high-risk patients after bariatric surgery. *JAMA*. 2011;305(23):2419-2426.

Magro DO, Geloneze B, Delfini R, Pareja BC, Callejas F, Pareja JC. Long-term weight regain after gastric bypass: A 5-year prospective study. *Obes Surg*. 2008;18:648-651.

Marceau P, Biron S, Hould FS, et al. Duodenal switch: Long-term results. *Obes Surg*. 2007;17:1421-1430.

Marre M, Shaw J, Brändle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med*. 2009;26(3):268-278.

Martin CK, Redman LM, Zhang J, et al. Lorcaserin, a 5-HT2C receptor agonist, reduces body weight by decreasing energy intake without influencing energy expenditure. *J Clin Endocrinol Metab*. 2011;96(3):837-845.

Martins C, Strømmen M, Stavne O a, Nossum R, Mårvik R, Kulseng B. Bariatric surgery versus lifestyle interventions for morbid obesity--changes in body weight, risk factors and comorbidities at 1 year. *Obes Surg*. 2011;21:841-849.

Masoomi H, Kim H, Reavis KM, Mills S, Stamos MJ, Nguyen NT. Analysis of Factors Predictive of Gastrointestinal Tract Leak in Laparoscopic and Open Gastric Bypass. *Arch Surg*. 2011;146(9):1048-1051.

Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes, Obes Metab*. 2014;16(7):636-644.

Mathus-Vliegen EMH, Alders PRH, Chuttani R, Scherpenisse J, Mathus- EMH, Centre AM. Outcomes of intragastric balloon placements in a private practice setting. 2015:302-307.

Matsuo Y, Oberbach A, Till H, et al. Impaired HDL function in obese adolescents: Impact of lifestyle intervention and bariatric surgery. *Obesity*. 2013;21(12):687-695.

Mayo Clinic. Gastric bypass surgeries: risks. http://www.mayoclinic.org/tests-procedures/bariatric-surgery/basics/risks/prc-20019138. Accessed September, 2014.

Mayo Clinic. Guide to Types of Weight Loss Surgery. http://www.mayoclinic.org/tests-procedures/bariatric-surgery/in-depth/weight-loss-surgery/art-20045334. Accessed January, 2015.

Mazure R A, Salgado G, Villarreal P, Cobo B, Valencia A, Culebras JM. Intragastric balloon and multidisciplinary team. *Nutr Hosp*. 2009;24(3):282-287.

Melissas J, Mouzas J, Filis D, et al. The intragastric balloon - Smoothing the path to bariatric surgery. *Obes Surg*. 2006;16(7):897-902.

Melton GB, Steele KE, Schweitzer M a., Lidor AO, Magnuson TH. Suboptimal weight loss after gastric bypass surgery: Correlation of demographics, comorbidities, and insurance status with outcomes. *J Gastrointest Surg*. 2008;12:250-255.

Messiah SE, Lopez-Mitnik G, Winegar D, et al. Changes in weight and co-morbidities among adolescents undergoing bariatric surgery: 1-year results from the Bariatric Outcomes Longitudinal Database. *Surg Obes Relat Dis*. 2013;9:503-513.

Micromedex Healthcare Series. RED BOOK® Online. Greenwood Village, CO: Truven Health Analytics, 2014. http://truvenhealth.com/. Accessed May, 2015.

Mingrone G, Greco a. V., Giancaterini a., Scarfone a., Castagneto M, Pugeat M. Sex hormone-binding globulin levels and cardiovascular risk factors in morbidly obese subjects before and after weight reduction induced by diet or malabsorptive surgery. *Atherosclerosis*. 2002;161:455-462.

Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes. *N Engl J Med*. 2012;366:1577-1585.

Miranda WR, Batsis J a., Sarr MG, et al. Impact of bariatric surgery on quality of life, functional capacity, and symptoms in patients with heart failure. *Obes Surg*. 2013;23:1011-1015.

Mognol P, Chosidow D, Marmuse J-P. Laparoscopic gastric bypass versus laparoscopic adjustable gastric banding in the super-obese: a comparative study of 290 patients. *Obes Surg*. 2005;15:76-81.

Mohamed ZK, Kalbassi MR, Boyle M, Small PK. Intra-gastric balloon therapy and weight reduction. *Surgeon*. 2008;6(4):210-212.

Mohos E, Schmaldienst E, Prager M. Quality of life parameters, weight change and improvement of co-morbidities after laparoscopic roux y gastric bypass and laparoscopic gastric sleeve resection-comparative study. *Obes Surg*. 2011;21:288-294.

Moon RC, Teixeira AF, DuCoin C, Varnadore S, Jawad M a. Comparison of cholecystectomy cases after Roux-en-Y gastric bypass, sleeve gastrectomy, and gastric banding. *Surg Obes Relat Dis*. 2014;10(1):64-68.

Müller MK, Wenger C, Schiesser M, Clavien PA, Weber M. Quality of life after bariatric surgery - A comparative study of laparoscopic banding vs. bypass. *Obes Surg*. 2008;18:1551-1557.

Murr MM, Martin T, Haines K, et al. A state-wide review of contemporary outcomes of gastric bypass in Florida: does provider volume impact outcomes? *Ann Surg*. 2007;245(5):699-706.

Mui WLM, Ng EKW, Tsung BYS, Lam CH, Yung MY. Impact on obesity-related illnesses and quality of life following intragastric balloon. *Obes Surg*. 2010;20(8):1128-1132.

Musella M, Milone M, Maietta P, et al. Bariatric surgery in elderly patients . A comparison between gastric banding and sleeve gastrectomy with fi ve years of follow up. *Int J Surg*. 2014;12:S69-S72.

Nadler EP, Youn H a., Ren CJ, Fielding G a. An update on 73 US obese pediatric patients treated with laparoscopic adjustable gastric banding: comorbidity resolution and compliance data. *J Pediatr Surg*. 2008;43:141-146.

Naef M, Naef U, Mouton W, Wagner H. Outcome and complications after laparoscopic Swedish adjustable gastric banding: 5-year results of a prospective clinical trial. *Obes Surg*. 2007;17:195-201.

Nanni G, Familiari P, Mor A, et al. Effectiveness of the transoral endoscopic vertical gastroplasty (TOGa®): A good balance between weight loss and complications, if compared with gastric bypass and biliopancreatic diversion. *Obes Surg*. 2012;22:1897-1902.

National Institutes of Health. Bariatric surgery for severe obesity. National Institute of Diabetes and Digestive and Kidney Diseases, Weight-control Information Network. March, 2009. http://win.niddk.nih.gov/publications/pdfs/prescription_medications.pdf. Accessed September, 2014.

National Institutes of Health. Prescription medications for the treatment of obesity. National Institute of Diabetes and Digestive and Kidney Diseases, Weight-control Information Network. April, 2013.

http://win.niddk.nih.gov/publications/pdfs/prescriptionmedications.pdf. Accessed September, 2014.

Nauck, M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care*. 2009;32(1):84-90.

Nelson DW, Blair KS, Martin MJ. Analysis of Obesity-Related Outcomes and Bariatric Failure Rates With the Duodenal Switch vs Gastric Bypass for Morbid Obesity. *Arch Surg*. 2012;147(9):847-854.

Nelson D, Porta R, Blair K, Carter P, Martin M. The duodenal switch for morbid obesity: Modification of cardiovascular risk markers compared with standard bariatric surgeries. *Am J Surg*. 2012;203(5):603-607.

Nguyen GC, Patel AM. Racial disparities in mortality in patients undergoing bariatric surgery in the USA. *Obes Surg*. 2013;23:1508-1514.

Nguyen NQ, Game P, Bessell J, et al. Outcomes of Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding. *World J Gastroenterol*. 2013;19(36):6035-6043.

Nguyen NT, Masoomi H, Laugenour K, et al. Predictive factors of mortality in bariatric surgery: Data from the Nationwide Inpatient Sample. *Surgery*. 2011;150(2):347-351.

Nguyen NT, Nguyen B, Smith B, Reavis KM, Elliott C, Hohmann S. Proposal for a bariatric mortality risk classification system for patients undergoing bariatric surgery. *Surg Obes Relat Dis*. 2013;9(2):239-246.

Nguyen NT, Hohmann S, Slone J, Varela E, Smith BR, Hoyt D. Improved bariatric surgery outcomes for Medicare beneficiaries after implementation of the medicare national coverage determination. *Arch Surg*. 2010;145(1):72-78.

Nguyen NT, Paya M, Stevens CM, Mavandadi S, Zainabadi K, Wilson SE. The relationship between hospital volume and outcome in bariatric surgery at academic medical centers. *Ann Surg*. 2004;240(4):586-593; discussion 593-594.

Nguyen NT, Slone J a, Nguyen X-MT, Hartman JS, Hoyt DB. A prospective randomized trial of laparoscopic gastric bypass versus laparoscopic adjustable gastric banding for the treatment of morbid obesity: outcomes, quality of life, and costs. *Ann Surg*. 2009;250(4):631-641.

Nicholas LH, Dimick JB. Bariatric Surgery in Minority Patients Before and After Implementation of a Centers of Excellence Program. *JAMA*. 2013;310(13), 1399–1400.

Nijamkin MP, Campa A, Samiri Nijamkin S, Sosa J. Comprehensive behavioral-motivational nutrition education improves depressive symptoms following bariatric surgery: A randomized, controlled trial of obese Hispanic Americans. *J Nutr Educ Behav.* 2013;45(6), 620–626.

Nijamkin MP, Campa A, Sosa J, Baum M, Himburg S, Johnson P. Comprehensive Nutrition and Lifestyle Education Improves Weight Loss and Physical Activity in Hispanic Americans Following Gastric Bypass Surgery: A Randomized Controlled Trial. *J Acad Nutr Diet*. 2012;112(3):382-390.

Nocca D, Guillaume F, Noel P, et al. Impact of laparoscopic sleeve gastrectomy and laparoscopic gastric bypass on HbA1c blood level and pharmacological treatment of type 2 diabetes mellitus in severe or morbidly obese patients. Results of a multicenter prospective study at 1 year. *Obes Surg*. 2011;21:738-743.

Nocca D, Nedelcu M, Nedelcu A, et al. Laparoscopic sleeve gastrectomy for late adolescent population. *Obes Surg*. 2014;24:861-865.

Nordstrand N, Hertel JK, Hofsø D, et al. A controlled clinical trial of the effect of gastric bypass surgery and intensive lifestyle intervention on nocturnal hypertension and the circadian blood pressure rhythm in patients with morbid obesity. *Surgery*. 2012;151(5):674-680.

Novo Nordisk. Product Backgrounders: Victoza. https://www.novomedlink.com/diabetes-videos/product-backgrounders/victoza-injection-conversation.html. Accessed May, 2015.

Obeid A, Long J, Kakade M, Clements RH, Stahl R, Grams J. Laparoscopic Roux-en-Y gastric bypass: long term clinical outcomes. *Surg Endosc*. 2012:3515-3520.

O'Brien PE, Brennan L, Laurie C, Brown W. Intensive medical weight loss or laparoscopic adjustable gastric banding in the treatment of mild to moderate obesity: Long-term follow-up of a prospective randomised trial. *Obes Surg*. 2013;23:1345-1353.

O'Brien PE, Dixon JB, Laurie C, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med*. 2006;144:625-633.

O'Brien PE, Sawyer SM, Laurie C, et al. Laparoscopic adjustable gastric banding in severely obese adolescents: A randomized trial. *JAMA*. 2010;303(6):519-526.

O'Neil PM, Smith SR, Weissman NJ, et al. Randomized Placebo-Controlled Clinical Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus: The BLOOM-DM Study. *Obesity*. 2012;20(7):1426-1436.

Obesity Action Coalition. Obesity statistics. http://www.obesityaction.org/understanding-obesity. Accessed September, 2014.

Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *J Am Med Assoc*. 2014;311:806-814.

Oliak D, Owens M, Schmidt HJ. Impact of Fellowship Training on the Learning Curve for Laparoscopic Gastric Bypass. *Obes Surg*. 2004;14:197-200.

Oliván B, Teixeira J, Bose M, et al. Effect of weight loss by diet or gastric bypass surgery on peptide YY3-36 levels. *Ann Surg*. 2009;249:948-953.

Olsen M. Respiratory Function in Superobese Patients before and after Bariatric Surgery- a Randomised Controlled Trial. *Open Obes J*. 2012;4:28-34.

Omana JJ, Nguyen SQ, Herron D, Kini S. Comparison of comorbidity resolution and improvement between laparoscopic sleeve gastrectomy and laparoscopic adjustable gastric banding. *Surg Endosc Other Interv Tech*. 2010;24(June 2001):2513-2517.

Ortega E, Morínigo R, Flores L, et al. Predictive factors of excess body weight loss 1 year after laparoscopic bariatric surgery. *Surg Endosc Other Interv Tech*. 2012;26:1744-1750.

Orexigen/Takeda, Inc. Important safety information for Contrave. http://contrave.com/?gclid=Cj0KEQjwhPaqBRDG2uiHzpKLi6ABEiQAk_XXiS1Nm_74U1u_Z44P6L9-LrK6yVZtLfZFRYOtPnNDXu8aAq1u8P8HAQ#inline-isi. Accessed May, 2015.

Orth WS, Madan AK, Taddeucci RJ, Coday M, Tichansky DS. Support group meeting attendance is associated with better weight loss. *Obes Surg*. 2008;18:391-394.

Østbye T, Stroo M, Eisenstein EL, Peterson B, Dement J. Is Overweight and Class I Obesity Associated with Increased Health Claims Costs? *Obesity (Silver Spring)*. 2014;22(4), 1179–1186.

Owers C, Ackroyd R. A study examining the complications associated with gastric banding. *Obes Surg*. 2013;23:56-59.

Padwal RS, Klarenbach SW, Wang X, et al. A simple prediction rule for all-cause mortality in a cohort eligible for bariatric surgery. *JAMA Surg*. 2013;148(12):1109-1115.

Padwal R, Klarenbach S, Wiebe N, et al. Bariatric surgery: A systematic review of the clinical and economic evidence. *J Gen Intern Med*. 2011;26:1183-1194.

Padwal RS, Rueda-Clausen CF, Sharma a M, et al. Weight Loss and Outcomes in Wait-listed, Medically Managed, and Surgically Treated Patients Enrolled in a Population-based Bariatric Program: Prospective Cohort Study. *Med Care*. 2014;52(3):208-215.

Palikhe G, Gupta R, Behera BN, Sachdeva N, Gangadhar P, Bhansali A. Efficacy of laparoscopic sleeve gastrectomy and intensive medical management in obese patients with type 2 diabetes mellitus. *Obes Surg*. 2014;24:529-535.

Paluszkiewicz R, Kalinowski P, Wróblewski T, et al. Prospective randomized clinical trial of laparoscopic sleeve gastrectomy versus open Roux-en-Y gastric bypass for the management of patients with morbid obesity. *Wideochirurgia i inne Tech mało inwazyjne*. 2012;7:225-232.

Papasavas PK, Hayetian FD, Caushaj PF, et al. Outcome analysis of laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Surg Endosc*. 2002;16:1653-1657.

Parikh MS, Shen R, Weiner M, Siegel N, Ren CJ. Laparoscopic bariatric surgery in super-obese patients (BMI>50) is safe and effective: A review of 332 patients. *Obes Surg*. 2005;15:858-863.

Parikh M, Dasari M, McMacken M, Ren C, Fielding G, Ogedegbe G. Does a preoperative medically supervised weight loss program improve bariatric surgery outcomes? A pilot randomized study. *Surg Endosc Other Interv Tech*. 2012;26(123):853-861.

Parikh M, Chung M, Sheth S, et al. Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do NOT meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker of success. *Ann Surg*. 2014;260(4):617-622; discussion 622-4.

Parikh M, Lo H, Chang C, Collings D, Fielding G, Ren C. Comparison of outcomes after laparoscopic adjustable gastric banding in African-Americans and whites. *Surg Obes Relat Dis*. 2006;2:607-610.

Peker Y, Coskun H, Bozkurt S, Cin N, Atak T, Genc H. Comparison of results of laparoscopic gastric banding and consecutive intragastric balloon application at 18 months: a clinical prospective study. *J Laparoendosc Adv Surg Tech A* 2011;21(6):471-475.

Perugini RA , Mason R, Czerniach DR, et al. Predictors of complication and suboptimal weight loss after laparoscopic Roux-en-Y gastric bypass: a series of 188 patients. *Arch Surg*. 2003;138(May 2003):541-545; discussion 545-546.

Peterli R, Borbély Y, Kern B, et al. Early results of the Swiss Multicentre Bypass or Sleeve Study (SM-BOSS): a prospective randomized trial comparing laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. *Ann Surg*. 2013;258(5):690-694; discussion 695.

Peterli R, Steinert RE, Woelnerhanssen B, et al. Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: A randomized, prospective trial. *Obes Surg*. 2012;22:740-748.

Pham S, Gancel A, Scotte M, et al. Comparison of the effectiveness of four bariatric surgery procedures in obese patients with type 2 diabetes: a retrospective study. *J Obes*. 2014;2014:638203.

Phillips E, Ponce J, Cunneen S a., et al. Safety and effectiveness of Realize adjustable gastric band: 3-year prospective study in the United States. *Surg Obes Relat Dis*. 2009;5(5):588-597.

Picot J, Jones J, Colquitt JL, et al..The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. *Health Technol Assess*. 2009;13(41):1-190, 215-357, iii-iv.

Pihlajamäki J, Grönlund S, Simonen M, et al. Cholesterol absorption decreases after Roux-en-Y gastric bypass but not after gastric banding. *Metabolism*. 2010;59(6):866-872.

Pohle-Krauza RJ, McCarroll ML, Pasini DD, Dan AG, Zografakis JG. Age and gender exert differential effects on blood lipids in patients after LAGB and LRYGB. *Surg Obes Relat Dis*. 2011;7(2):170-175.

Pollack A. AMA recognizes obesity as a disease. New York Times. June 18, 2013: http://www.nytimes.com/2013/06/19/business/ama-recognizes-obesity-as-a-disease.html?_r=0.

Ponce J, Woodman G, Swain J, et al. The REDUCE pivotal trial: a prospective, randomized controlled pivotal trial of a dual intragastric balloon for the treatment of obesity. *Surg Obes Relat Dis*. 2014:1-8.

Ponce J, Quebbemann BB, Patterson EJ. Prospective, randomized, multicenter study evaluating safety and efficacy of intragastric dual-balloon in obesity. *Surg Obes Relat Dis*. 2012;9(2):290-295.

Pontiroli AE, Fossati A, Vedani P, et al. Post-surgery adherence to scheduled visits and compliance, more than personality disorders, predict outcome of bariatric restrictive surgery in morbidly obese patients. *Obes Surg*. 2007;17:1492-1497.

Pontiroli AE, Morabito A. Long-term prevention of mortality in morbid obesity through bariatric surgery. a systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. *Ann Surg*. 2011;253:484-487.

Pournaras DJ, Jafferbhoy S, Titcomb DR, et al. Three hundred laparoscopic Roux-en-Y gastric bypasses: Managing the learning curve in higher risk patients. *Obes Surg*. 2010;20(September 2008):290-294.

Prachand VN, DaVee RT, Alverdy JC. Duodenal Switch Provides Superior Weight Loss in the Super-Obese (BMI ≥50kg/m2) Compared With Gastric Bypass. *Ann Surg*. 2006;244(4):611-619.

Prevot F, Verhaeghe P, Pequignot A, et al. Two lessons from a 5-year follow-up study of laparoscopic sleeve gastrectomy: Persistent, relevant weight loss and a short surgical learning curve. *Surg (United States)*. 2014;155:292-299.

Puglisi F, Antonucci N, Capuano P, et al. Intragastric balloon and binge eating. *Obes Surg*. 2007;17(4):504-509.

Puzziferri N, Nakonezny P a, Livingston EH, Carmody TJ, Provost D a, Rush a J. Variations of weight loss following gastric bypass and gastric band. *Ann Surg*. 2008;248(2):233-242.

Puzziferri N, Roshek TB, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term Follow-up After Bariatric Surgery A Systematic Review. *JAMA*. 2014;312(9):934-942.

Raffaelli M, Guidone C, Callari C, Iaconelli A, Bellantone R, Mingrone G. Effect of gastric bypass versus diet on cardiovascular risk factors. *Ann Surg*. 2014;259(4):694-699.

Ramón JM, Salvans S, Crous X, et al. Effect of Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy on Glucose and Gut Hormones: A Prospective Randomised Trial. *J Gastrointest Surg*. 2012;16:1116-1122.

Rattue P. EndoBarrier Re-Implantation Feasible. May 4, 2012: http://www.medicalnewstoday.com/articles/245022.php. Accessed January, 2015.

Ray EC, Nickels MW, Sayeed S, et al. Predicting success after gastric bypass: The role of psychosocial and behavioral factors. *Surgery*. 2003;134:555-564.

Raziel A, Sakran N, Szold A, et al. Mid-term follow-up after laparoscopic sleeve gastrectomy in obese adolescents. *Isr Med Assoc J*. 2014;16(1):37-41.

ReShape Medical. ReShape Medical® submits PMA application to FDA for non-surgical weight loss device. July 1, 2014. http://reshapemedical.com/articles/2014/reshape-medical-submits-pma-application-to-fda-for-non-surgical-weight-loss-device/. Accessed, May 2015.

Ricci G, Bersani G, Rossi A, Pigò F, De Fabritiis G, Alvisi V. Bariatric therapy with intragastric balloon improves liver dysfunction and insulin resistance in obese patients. *Obes Surg*. 2008;18(11):1438-1442.

Risstad H, Søvik TT, Engström M, et al. Five-year outcomes after laparoscopic gastric bypass and laparoscopic duodenal switch in patients with body Mass index of 50 to 60: a randomized clinical trial [published online ahead of print February 4, 2015]. *JAMA Surg*. 2015 Feb 4. doi: 10.1001/jamasurg.2014.3579.

Rodriguez L, Reyes E, Fagalde P, et al. Pilot clinical study of an endoscopic, removable duodenal-jejunal bypass liner for the treatment of type 2 diabetes. *Diabetes Technol Ther*. 2009;11(11):725-732.

Roman S, Napoléon B, Mion F, et al. Intragastric balloon for "non-morbid" obesity: A retrospective evaluation of tolerance and efficacy. *Obes Surg*. 2004;14(4):539-544.

Romero F, Nicolau J, Flores L, et al. Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. *Surg Endosc*. 2012;26:2231-2239.

Romy S, Donadini A, Giusti V, Suter M. Roux-en-Y gastric bypass vs gastric banding for morbid obesity: a case-matched study of 442 patients. *Arch Surg*. 2012;147(5):460-466.

Roslin MS, Dudiy Y, Brownlee A, Weiskopf J, Shah P. Response to glucose tolerance testing and solid high carbohydrate challenge: Comparison between Roux-en-Y gastric bypass, vertical sleeve gastrectomy, and duodenal switch. *Surg Endosc Other Interv Tech*. 2014;28:91-99.

Roslin MS, Dudiy Y, Weiskopf J, Damani T, Shah P. Comparison between RYGB, DS, and VSG effect on glucose homeostasis. *Obes Surg*. 2012;22:1281-1286.

Rossi A, Bersani G, Ricci G, Petrini C, DeFabritiis G, Alvisi V. Intragastric balloon insertion increases the frequency of erosive esophagitis in obese patients. *Obes Surg*. 2007;17(10):1346-1349.

Rothberg AE, McEwen LN, Kraftson AT, et al. The impact of weight loss on health-related quality of life: implications for cost-effectiveness analyses. *Qual Life Res*. 2014;23(4):1371-1376.

Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): A randomised controlled trial. *DiabetologiA* 2009;52(10):2046-2055.

Sabbagh C, Verhaeghe P, Dhahri A, et al. Two-year results on morbidity, weight loss and quality of life of sleeve gastrectomy as first procedure, sleeve gastrectomy after failure of gastric banding and gastric banding. *Obes Surg*. 2010;20:679-684.

Sallet J A, Marchesini JB, Paiva DS, et al. Brazilian multicenter study of the intragastric balloon. *Obes Surg*. 2004;14(7):991-998.

Sarr MG, Billington CJ, Brancatisano R, et al. The EMPOWER Study: Randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity. *Obes Surg*. 2012;22(11):1771-1782.

Sarwer DB, Moore RH, Spitzer JC, Wadden T a., Raper SE, Williams NN. A pilot study investigating the efficacy of postoperative dietary counseling to improve outcomes after bariatric surgery. *Surg Obes Relat Dis*. 2012;8(5):561-568.

Sarwer DB, Wadden T a., Moore RH, et al. Preoperative eating behavior, postoperative dietary adherence, and weight loss after gastric bypass surgery. *Surg Obes Relat Dis*. 2008;4:640-646.

Saunders JK, Ballantyne GH, Belsley S, et al. 30-Day readmission rates at a high volume bariatric surgery center: Laparoscopic adjustable gastric banding, laparoscopic gastric bypass, and vertical banded gastroplasty-Roux-en-Y gastric bypass. *Obes Surg*. 2007;17:1171-1177.

Schaeffer DF, Rusnak CH, Amson BJ. Laparoscopic Roux-en-Y gastric bypass surgery: initial results of 120 consecutive patients at a single British Columbia surgical center. *Am J Surg*. 2008;195:565-569.

Schauer P, Ikramuddin S, Hamad G, Gourash W. The learning curve for laparoscopic Roux-en-Y gastric bypass is 100 cases. *Surg Endosc*. 2003;17:212-215.

Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric Surgery versus Intensive medical therapy for diabetes --3-year outcomes. *N Engl J Med*. 2014;370(21):2002-2013.

Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med*. 2012;366(17):1567-1576.

Schouten R, Rijs CS, Bouvy ND, et al. A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. *Ann Surg*. 2010;251(2):236-43.

Scopinaro N, Adami GF, Papadia FS, et al. Effects of biliopanceratic diversion on type 2 diabetes in patients with BMI 25 to 35. *Ann Surg*. 2011;253(4):699-703.

Serrot FJ, Dorman RB, Miller CJ, et al. Comparative effectiveness of bariatric surgery and nonsurgical therapy in adults with type 2 diabetes mellitus and body mass index <35 kg/m2. *Surgery*. 2011;150(4):684-691.

Shapiro K, Patel S, Abdo Z, Ferzli G. Laparoscopic adjustable gastric banding: Is there a learning curve? *Surg Endosc Other Interv Tech*. 2004;18:48-50.

Shikora SA, Kim JJ, Tarnoff ME, Raskin E, Shore R. Laparoscopic Roux-en-Y Gastric Bypass: Results and learning curve of a high-volume academic program. *Arch Surg*. 2015;140(4): 362-367.

Silberhumer GR, Miller K, Pump A, et al. Long-term results after laparoscopic adjustable gastric banding in adolescent patients: follow-up of the Austrian experience. *Surg Endosc*. 2011;25:2993-2999.

Silecchia G, Bacci V, Bacci S, et al. Reoperation after laparoscopic adjustable gastric banding: analysis of a cohort of 500 patients with long-term follow-up. *Surg Obes Relat Dis*. 2008;4:430-436.

Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. *J Intern Med*. 2013;273:219-234.

Sjöström L, Narbro K, Sjöström D, et al. Effects of bariatric surgery on mortality in Swedish Obese Subjects. *N Engl J Med*. 2007;357(8):741-752.

Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA*. 2014;311(22):2297-2304.

Sjöström L, Peltonen M, Jacobson P, et al. Bariatric Surgery and Long-term Cardiovascular Events. *JAMA*. 2012;307(1):56-65.

Skroubis G, Karamanakos S, Sakellaropoulos G, Panagopoulos K, Kalfarentzos F. Comparison of early and late complications after various bariatric procedures: Incidence and treatment during 15 years at a single institution. *World J Surg*. 2011;35:93-101.

Smith MD, Patterson E, Wahed AS, et al. Can technical factors explain the volume-outcome relationship in gastric bypass surgery? *Surg Obes Relat Dis*. 2013;9(5):623-629.

Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med.* 2010;363(3):245-256.

Smith SR, Prosser W a, Donahue DJ, Morgan ME, Anderson CM, Shanahan WR. Lorcaserin (APD356), a selective 5-HT(2C) agonist, reduces body weight in obese men and women. *Obesity (Silver Spring)*. 2009;17(3):494-503.

Sockalingam S, Cassin S, Crawford S a., et al. Psychiatric predictors of surgery non-completion following suitability assessment for bariatric surgery. *Obes Surg*. 2013;23:205-211.

Søvik TT, Taha O, Aasheim ET, et al. Randomized clinical trial of laparoscopic gastric bypass versus laparoscopic duodenal switch for superobesity. *Br J Surg*. 2010;97:160-166.

Søvik TT, Aasheim ET, Kristinsson J, et al. Establishing laparoscopic Roux-en-Y gastric bypass: Perioperative outcome and characteristics of the learning curve. *Obes Surg*. 2009;19:158-165.

Søvik TT, Aasheim ET, Taha O, et al. Weight Loss, Cardiovascular risk factors and quality of life after gastric bypass and duodenal switch: A randomized trial. *Ann Intern Med*. 2011;155(5):281-291.

Spaniolas K, Trus TL, Adrales GL, Quigley MT, Pories WJ, Laycock WS. Early morbidity and mortality of laparoscopic sleeve gastrectomy and gastric bypass in the elderly: a NSQIP analysis. *Surg Obes Relat Dis*. 2014;10(4):584-588.

Spivak H, Abdelmelek MF, Beltran OR, Ng AW, Kitahama S. Long-term outcomes of laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass in the United States. *Surg Endosc*. 2012;26:1909-1919.

Stephens DJ, Saunders JK, Belsley S, et al. Short-term outcomes for super-super obese (BMI > or =60 kg/m2) patients undergoing weight loss surgery at a high-volume bariatric surgery center: laparoscopic adjustable gastric banding, laparoscopic gastric bypass, and open tubular gastric bypass. *Surg Obes Relat Dis*. 2008;4(3):408-415.

Still CD, Wood GC, Chu X, et al. Clinical factors associated with weight loss outcomes after Roux-en-Y gastric bypass surgery. *Obesity (Silver Spring)*. 2014;22(3):888-894.

Strain GW, Gagner M, Pomp A, et al. Comparison of weight loss and body composition changes with four surgical procedures. *Surg Obes Relat Dis*. 2009;5(5):582-587.

Strain GW, Gagner M, Inabnet WB, Dakin G, Pomp A. Comparison of effects of gastric bypass and biliopancreatic diversion with duodenal switch on weight loss and body composition 1-2 years after surgery. *Surg Obes Relat Dis*. 2007;3:31-36.

Suter M, Donadini A, Romy S, Demartines N, Giusti V. Laparoscopic Roux-en-Y gastric bypass: significant long-term weight loss, improvement of obesity-related comorbidities and quality of life. *Ann Surg*. 2011;254(2):267-273.

Takihata M, Nakamura A, Aoki K, et al. Comparison of intragastric balloon therapy and intensive lifestyle modification therapy with respect to weight reduction and abdominal fat distribution in super-obese Japanese patients. *Obes Res Clin Pract*. 2014;8(4):e331-e338.

Tarnoff M, Rodriguez L, Escalona A, et al. Open label, prospective, randomized controlled trial of an endoscopic duodenal-jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery. *Surg Endosc Other Interv Tech*. 2009;23(3):650-656.

Tayyem RM, Obondo C, Ali A Short-term outcome and quality of life of endoscopically placed gastric balloon and laparoscopic adjustable gastric band. *Saudi J Gastroenterol.* 2011;17(6):400-405.

Te Riele WW, Sze YK, Wiezer MJ, van Ramshorst B. Conversion of failed laparoscopic gastric banding to gastric bypass as safe and effective as primary gastric bypass in morbidly obese patients. *Surg Obes Relat Dis*. 2008;4(6):735-739.

Tedesco M, Hua WQ, Lohnberg J a., Bellatorre N, Eisenberg D. A prior history of substance abuse in veterans undergoing bariatric surgery. *J Obes*. 2013;2013.

The Medical Letter on Drugs and Therapeutics. Diet, drugs, and surgery for weight loss. http://secure.medicalletter.org/article-share?a=1462a&p=tml&title=Diet,%20Drugs,%20and%20Surgery%20for%20Weight%20Loss&cannotaccesstitle=1. Accessed May, 2015.

Toelle P, Peterli R, Zobel I, Noppen C, Christoffel-Courtin C, Peters T. Risk factors for secondary hyperparathyroidism after bariatric surgery: A comparison of 4 different operations and of vitamin D-receptor-polymorphism. *Exp Clin Endocrinol Diabetes*. 2012;120(10):629-634.

Topart P, Becouarn G, Ritz P. Comparative early outcomes of three laparoscopic bariatric procedures: Sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion with duodenal switch. *Surg Obes Relat Dis*. 2012;8(3):250-254.

Topart P, Becouarn G, Ritz P. Weight loss is more sustained after biliopancreatic diversion with duodenal switch than Roux-en-Y gastric bypass in superobese patients. *Surg Obes Relat Dis*. 2013;9(4):526-530.

Torrente JE, Cooney RN, Rogers AM, Hollenbeak CS. Importance of hospital versus surgeon volume in predicting outcomes for gastric bypass procedures. *Surg Obes Relat Dis*. 2013;9(2):247-252.

Treadwell J, Sun F, Bruening W, et al. Bariatric Surgery in Pediatric Patients. ECRI Institute. August, 20, 2007: http://www.hca.wa.gov/hta/documents/bariatric_pediatric.pdf. Accessed September, 2014.

Tsoli M, Chronaiou A, Kehagias I, Kalfarentzos F, Alexandrides TK. Hormone changes and diabetes resolution after biliopancreatic diversion and laparoscopic sleeve gastrectomy: A comparative prospective study. *Surg Obes Relat Dis*. 2013;9(5):667-677.

UKHealthCentre. Gastric Balloon London & UK. http://www.healthcentre.org.uk/weight-loss-surgery/weight-loss-surgery-gastric-balloon.html. Accessed May, 2015.

University of Illinois Bariatric Surgery Program. Roux-en-Y Gastric Bypass (RYGB). 2015: http://hospital.uillinois.edu/Patient_Care_Services/Bariatric_Surgery/Our_Services/Roux-en-Y_Gastric_Bypass_%28RYGB%29.html. Accessed January, 2015.

US Bureau of Labor Statistics. Consumer Price Index. 2014. http://www.bls.gov/cpi/cpid1501.pdf. Accessed May, 2015.

US Drug Enforcement Administration. 21 CFR Part 1308, Placement of Lorcaserin into Schedule IV. https://www.federalregister.gov/articles/2013/05/08/2013-10895/schedules-of-controlled-substances-placement-of-lorcaserin-into-schedule-iv. Accessed, May 2015a.

US Drug Enforcement Administration. Drug Fact Sheets. http://www.dea.gov/druginfo/concerns.shtml. Accessed, May 2015b.

US Food and Drug Administration. FDA expands use of banding system for weight loss. February 16, 2011: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm245617.htm. Accessed September, 2014.

US Food and Drug Administration. FDA approves first-of-kind device to treat obesity. January 14, 2015: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430223.htm. Accessed May, 2015.

Van Nieuwenhove Y, Dambrauskas Z, Campillo-Soto a., et al. Preoperative Very Low-Calorie Diet and Operative Outcome After Laparoscopic Gastric Bypass: A Randomized Multicenter Study. *Arch Surg*. 2011;146(11):1300-1305.

Viana EC, Araujo-Dasilio KL, Miguel GPS, et al. Gastric bypass and sleeve gastrectomy: The same impact on IL-6 and TNF-α. Prospective clinical trial. *Obes Surg*. 2013;23:1252-1261.

Vidal J, Ibarzabal a., Romero F, et al. Type 2 diabetes mellitus and the metabolic syndrome following sleeve gastrectomy in severely obese subjects. *Obes Surg*. 2008;18(9):1077-1082.

Vidal J, Ibarzabal a, Nicolau J, et al. Short-term effects of sleeve gastrectomy on type 2 diabetes mellitus in severely obese subjects. *Obes Surg*. 2007;17(8):1069-1074.

Vidal P, Ramón JM, Goday A, et al. Laparoscopic gastric bypass versus laparoscopic sleeve gastrectomy as a definitive surgical procedure for morbid obesity. Mid-term results. *Obes Surg*. 2013;23(3):292-299.

Vilarrasa N, De Gordejuela AGR, Gómez-Vaquero C, et al. Effect of bariatric surgery on bone mineral density: Comparison of gastric bypass and sleeve gastrectomy. *Obes Surg*. 2013;23:2086-2091.

Vix M, Diana M, Liu KH, et al. Evolution of glycolipid profile after sleeve gastrectomy vs. Roux-en-Y gastric bypass: Results of a prospective randomized clinical trial. *Obes Surg*. 2013;23:613-621.

Von Mach MA., Stoeckli R, Bilz S, Kraenzlin M, Langer I, Keller U. Changes in bone mineral content after surgical treatment of morbid obesity. *Metabolism*. 2004;53(7):918-921.

Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)*. 2011;19(1):110-120.

Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *O Int J Obes (Lond)*. 2013;37(11):1443-1451.

Wahlroos S, Phillips ML, Lewis MC, et al. Rapid significant weight loss and regional lipid deposition: Implications for insulin sensitivity. *Obes Res Clin Pract*. 2007;1(1):7-16.

Wang BC, Wong ES, Alfonso-Cristancho R, et al. Cost-effectiveness of bariatric surgical procedures for the treatment of severe obesity. *Eur J Health Econ.* 2014;15(3):253–63.

Weber M, Müller MK, Bucher T, et al. Laparoscopic gastric bypass is superior to laparoscopic gastric banding for treatment of morbid obesity. *Ann Surg*. 2004;240(6):975-982; discussion 982-983.

Weineland S, Arvidsson D, Kakoulidis TP, Dahl J. Acceptance and commitment therapy for bariatric surgery patients, a pilot RCT. *Obes Res Clin Pract*. 2012;6(1):e21-e30.

Weiner JP, Goodwin SM, Chang H-Y, et al. Impact of bariatric surgery on health care costs of obese persons: a 6-year follow-up of surgical and comparison cohorts using health plan data. *JAMA Surg*. 2013;148(6):555-562.

Weiner R a., El-Sayes I a., Theodoridou S, Weiner SR, Scheffel O. Early post-operative complications: Incidence, management, and impact on length of hospital stay. A retrospective comparison between laparoscopic gastric bypass and sleeve gastrectomy. *Obes Surg*. 2013;23:2004-2012.

Weller WE, Rosati C, Hannan EL. Relationship Between Surgeon and Hospital Volume and Readmission after Bariatric Operation. *J Am Coll Surg*. 2007;204:383-391.

Widhalm K, Fritsch M, Widhalm H, et al. Bariatric surgery in morbidly obese adolescents: long-term follow-up. *Int J Pediatr Obes*. 2011;6 Suppl 1(July):65-69.

Winslow DH, Bowden CH, DiDonato KP, McCullough P A A Randomized, Double-Blind, Placebo-Controlled Study of an Oral, Extended-Release Formulation of Phentermine/Topiramate for the Treatment of Obstructive Sleep Apnea in Obese Adults. *Sleep*. 2012.

Wittgrove a C, Clark GW. Laparoscopic gastric bypass, Roux-en-Y- 500 patients: technique and results, with 3-60 month follow-up. *Obes Surg*. 2000;10(3):233-239.

Woelnerhanssen B, Peterli R, Steinert RE, Peters T, Borbély Y, Beglinger C. Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: Comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomya prospective randomized trial. *Surg Obes Relat Dis*. 2011;7(5):561-568.

Wong SKH, Mui WLM, Ng EKW. Development of bariatric surgery: The effectiveness of a multi-disciplinary weight management programme in Hong Kong. *Ann Acad Med Singapore*. 2009;38(1):9-14.

Woodard G a., Peraza J, Bravo S, Toplosky L, Hernandez-Boussard T, Morton JM. One year improvements in cardiovascular risk factors: A comparative trial of laparoscopic Roux-en-Y gastric bypass vs. adjustable gastric banding. *Obes Surg*. 2010;20:578-582.

World Health Organization. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet.* 2004;363:157–63.

Yong W, Shibo W, Jingang L. Remission of insulin resistance in type 2 diabetic patients after gastric bypass surgery or exenatide therapy. *Obes Surg*. 2012;22:1060-1067.

Yousseif A, Emmanuel J, Karra E, et al. Differential effects of laparoscopic sleeve gastrectomy and laparoscopic gastric bypass on appetite, circulating acyl-ghrelin, peptide YY3-36 and active GLP-1 levels in non-diabetic humans. *Obes Surg*. 2014;24:241-252.

Zachariah SK, Chang P-C, Ooi ASE, Hsin M-C, Kin Wat JY, Huang CK. Laparoscopic sleeve gastrectomy for morbid obesity: 5 years experience from an Asian center of excellence. *Obes Surg*. 2013;23:939-946.

Zacharoulis D, Sioka E, Papamargaritis D, et al. Influence of the learning curve on safety and efficiency of laparoscopic sleeve gastrectomy. *Obes Surg*. 2012;22:411-415.

Zerrweck C, Sepúlveda EM, Maydón HG, et al. Laparoscopic gastric bypass vs. sleeve gastrectomy in the super obese patient: Early outcomes of an observational study. *Obes Surg*. 2014;24:712-717.

Zhang N, Maffei A, Cerabona T, Pahuja A, Omana J, Kaul A. Reduction in obesity-related comorbidities: Is gastric bypass better than sleeve gastrectomy? *Surg Endosc Other Interv Tech*. 2013;27:1273-1280.

Zinman F, Gerich J, Buse JB, Lewin A, Schwartz S, Blonde L. Efficacy and Safety of the Human Liraglutide in Combination With Metformin and Thiazolidinedione in Patients With Type 2 Diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009;32(7):1224-1230.

Zuegel NP, Lang R a., Hüttl TP, et al. Complications and outcome after laparoscopic bariatric surgery: LAGB versus LRYGB. *Langenbeck's Arch Surg*. 2012;397:1235-1241.