Washington State Health Care Authority

Health Technology Assessment

Bariatric Surgery

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Bariatric Surgery

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Table of Contents

List of Figures

List of Tables

List of Acronyms

ACS	American College of Surgeons
ACT	Acceptance and commitment therapy
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
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
COE	Center of Excellence
DS	Duodenal Switch
EWL	Excess weight loss
GERD	Gastroesophageal reflux disease
HrQoL	Health-related quality of life
HR	Hazard ratio
LABS	Longitudinal Assessment of Bariatric Surgery
LAGB	Laparoscopic adjustable gastric band
LCD	Local Coverage decision
MBSAQIP	Metabolic Bariatric Surgery Accreditation and Quality Improvement Program
NCD	National Coverage Determination
NICE	National Institute for Health and Care Excellence
NS	Not significant
OR	Odds ratio
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RYGB	Roux-en-Y gastric bypass
SOS	Swedish Obese Subjects
TAU	Treatment as usual
VLCD	Very low calorie diet
VSG	Vertical sleeve gastrectomy
WHO	World Health Organization

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit health care research organization dedicated to improving the interpretation and application of evidence in the health care system.

There are several features of ICER's focus and methodology that distinguish it from other health care research organizations:

- Commitment to aiding patients, clinicians, and insurers in the application and use of comparative effectiveness information through various implementation avenues, including its core programs, the New England Comparative Effectiveness Public Advisory Council (CEPAC; cepac.icer-review.org) and the California Technology Assessment Forum (CTAF; www.ctaf.org).

- Focus on implementation and evaluation of ICER research to create innovative decision support tools, insurance benefit designs, and clinical/payment policy.

- Deep engagement throughout the process with all stakeholders including patients, clinicians, manufacturers, purchasers, and payers.

- Inclusion of economic modeling in our research, and use of an integrated rating system for comparative clinical effectiveness and comparative value to guide health care decisions.

- ICER's independent mission is funded through a diverse combination of sources; funding is not accepted from manufacturers or private insurers to perform reviews of specific technologies. A full list of funders, as well more information on ICER's mission and policies, can be found at www.icer-review.org.

Acknowledgements

Executive Summary

Introduction

It is estimated that 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, hypertension, cardiovascular disease, high blood pressure, and sleep apnea. Obesity and its sequelae are estimated to generate $147 billion in health care costs in the U.S. 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, many of which have been shown to pose significant health risks of their own (National Institutes of Health, 2013). More recently, options for surgical intervention have 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 U.S. 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 laparoscopic approach. The choice of procedure primarily depends 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).

Clinical interest in expanding the use of bariatric surgery to a broader set of individuals remains high. 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 of 1,136 long-term studies (2.6%) 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. For example, a 5-year follow-up study after gastric bypass surgery documented an average regain of 80% of the body mass index (BMI) lost following surgery (Magro, 2008); nearly 20% of patients with a pre-operative BMI >40 had failed to achieve the required reductions in excess body weight by year 4 of follow-up, double the rate observed at year 2. Other studies have documented more modest weight regain levels; however, the lack of consistent long-term data is problematic for understanding the true trajectory of weight following bariatric surgery.

As the Washington State Health Care Authority reviews its coverage policy for bariatric surgery, it is therefore timely to assess the evidence on the clinical benefits and cost-effectiveness of common weight loss procedures across all relevant populations, including those defined by level of obesity, age, and presence of specific types of comorbidity.

Bariatric Surgical Procedures of Interest

Roux-en-Y Gastric Bypass (RYGB)

Roux-en-Y gastric bypass (RYGB) is the most commonly performed bariatric procedure worldwide (ASMBS, 2015).   RYGB can be performed laparoscopically, robotically, or openly and has a typical duration that ranges from one-and-a-half to four hours.

Figure ES-1: Roux-en-Y Gastric Bypass
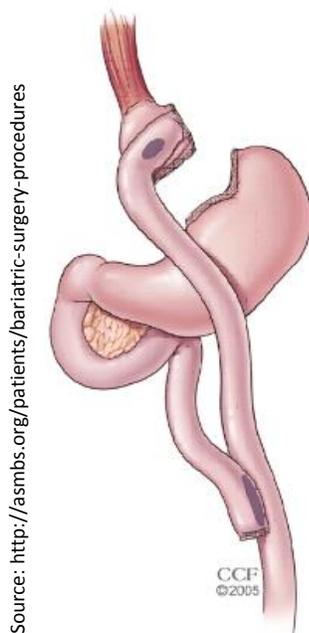
Source: http://asmbs.org/patients/bariatric-surgery-procedures

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 is intended to restrict food intake and promote satiety after small amounts 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 consists of 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. In addition to potential complications, RYGB has a few disadvantages, including the irreversibility of the procedure and its impedance on a patient's ability to absorb nutrients. Patients will need to take nutrient supplements for the remainder of their lives and monitor their intake of carbohydrates to avoid gastric discomfort, vomiting and diarrhea.

Biliopancreatic Diversion/Duodenal Switch (BPD/DS)

Biliopancreatic diversion is commonly performed on so-called "super-obese" individuals--those with a BMI of 50 kg/m2 or greater (Mayo Clinic, 2015). Similar to sleeve gastrectomy, 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 which 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 RYGB, the intestine length from stomach to colon is much shorter in BPD (ASMBS, 2015).

Figure ES-2: Biliopancreatic Diversion/Duodenal Switch

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.

Patients typically remain in the hospital for four to seven nights after BPD and take three to four weeks to recover. Because BPD/DS is a malabsorptive procedure, patients are at risk of developing nutrient deficiencies and will need 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 3-4 loose bowel movements a day. Nutrient deficiency conditions such as night blindness, iron deficiency anemia, beriberi, osteoporosis, and protein energy malnutrition may also occur.

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

Figure ES-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 by means of 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 1-2 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 are infrequent but can include hemorrhage, port infection, band infection, obstruction, nausea, vomiting, band erosion into the stomach, esophageal dilation, and inadequate weight loss.

Figure ES-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 for complications related to a longer procedure, have an excessively large liver, or have extensive scar tissue are considered possible candidates for sleeve gastrectomy (Cleveland Clinic, 2015). Once weight loss occurs, the liver decreases in size and the risk of surgery-related complications reduces. Patients may then return to the hospital to undergo gastric bypass as a second stage procedure.

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 1-2 weeks. VSG is not a malabsorptive procedure so there is less risk of nutrient deficiencies postoperatively. Potential complications include bleeding, infection, injury to other organs, conversion to an open procedure, and leakage from the staple line that divides the stomach (Cleveland Clinic, 2015).

Appraisal Scope

This project involved a systematic review of the published literature on the use of bariatric surgery for the four types of procedures that are most commonly utilized in the U.S.: 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). Evidence specifically in pediatric populations was obtained in order to build on a review conducted for the Health Care Authority in 2007, which examined studies published through June 2007 (ECRI Institute, 2007).

Key Questions

The following key questions were felt to be of primary importance for this review:

1) What is the comparative clinical effectiveness of bariatric surgery procedures versus conventional weight-loss management in:
    a. Adults (i.e., age 21 years and older)?
    b. Children (age <21), on an overall basis and by specific age groups (i.e., 18-20, 13-17, 12 or less)?

2) What components of the management of patients undergoing bariatric surgery (e.g., selection of candidates for surgery, multi-disciplinary care team, pre- and/or post-procedure counseling and support) appear to be correlated with higher levels of "treatment success" (e.g., sustained weight loss, reduction in comorbidity burden, etc.)?

3) What are the potential short- and long-term harms of bariatric surgery procedures, including rates of procedure-specific and general surgical complications, longer-term morbidity, mortality, and requirements for procedure revision and/or reversal?

4) What is the differential effectiveness and safety of bariatric surgery procedures according to health-system and/or program factors such as:
   a. Surgeon experience
   b. Procedure volume
   c. Certification of surgery center
   d. Members of core team
   e. Type of pre-procedure preparation/post-procedure support

5) What is the differential effectiveness and safety of bariatric surgery procedures according to patient and/or clinical factors such as:
   a. Age (both chronological and physiologic/skeletal)
   b. Gender
   c. Race/ethnicity
   d. BMI (assessed as both continuous and categorical variable)
   e. Presence of comorbidities (e.g., hypertension, type 2 diabetes)
   f. Prior event history (e.g., myocardial infarction, stroke)
   g. Smoking status
   h. Psychosocial health
   i. Pre/post procedure adherence with program recommendations

6) What are the costs and cost-effectiveness of the major bariatric surgery procedures of focus in this evidence review?

Analytic Framework

The analytic framework for this project is depicted below. There were expected limitations on the available evidence in terms of (a) comprehensive comparisons of all four procedures, and (b) long-term data on effectiveness and potential harms. As such, judgments about the effectiveness of these interventions rested predominantly upon individual consideration of each type of surgery and its relevant comparators, evaluation of procedure-specific risks, and linkage of shorter-term outcomes to higher-quality data on long-term effects where available. Additional details on the parameters and criteria used for the literature search, the types of comparative studies and case series allowed, as well as the resulting yield of published evidence can be found in the full report.

Figure ES-5: Analytic Framework for Bariatric Surgery

Study Quality

We used criteria published by the U.S. Preventive Services Task Force to assess the quality of randomized control trials (RCTs) and comparative cohort studies, using the categories "good," "fair," or "poor." Guidance for quality ratings using these criteria is presented below (AHRQ, 2008), as is a description of any modifications we made to these ratings specific to the purposes of this review. Note that case series are not considered as part of this rating system – because of the lack of comparator, these were universally considered to be of poor quality.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); 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, for RCTs, intention to treat analysis is used. Specifically for this review, target or mean/median duration of follow-up did not appreciably differ within study groups.*

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.*

Results

Evidence Quality

While the comparative evidence base for either head-to-head comparisons of bariatric procedures or comparisons of bariatric surgery to nonsurgical interventions has grown considerably over time, major challenges with the quality and applicability of available studies remains. Of the 179 comparative studies identified for this evaluation, we rated only 26 (15%) to be of good quality, based on comparable groups at baseline, comparable duration of follow-up, and limited sample attrition. An additional 74 studies (41%) were rated fair quality; issues with comparability, duration of follow-up, and/or attrition were identified in these studies, but attempts were made to control for confounding in the analytic methods (e.g., survival analysis techniques, multivariate regression). However, we considered another 79 studies (44%) to be of poor quality because at least one key quality issue was present and not adequately addressed in either study design or analysis.

Specific quality issues with the evidence were as follows. Treatment groups were often imbalanced with respect to baseline characteristics with great potential to influence outcomes. For example, we considered any difference in mean pre-operative BMI greater than 3 increments to be potentially

clinically significant. This was not only frequently encountered, but seldom controlled for in statistical analyses of outcome, even if that outcome was related to body weight or BMI. Many studies considered the within-subject change in BMI and other weight-related measures to be the most important outcomes of interest, and considered that justification for allowing some level of imbalance. No statistical differences were found in other studies even when large absolute differences were observed, but this appears to be a function of small sample size and consequent lack of statistical power to detect baseline differences.

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. Regarding the former, groups defined by surgical approach were often followed for different lengths of time because the procedures were performed by different groups or at different centers. In other cases, the difference in follow-up may have been planned—some studies focused on nutritional and/or metabolic outcomes after a certain threshold of weight loss, which frequently occurred over much longer period of time in nonsurgical control groups relative to surgical intervention (del Genio, 2007; Alam, 2011). In any case, no attempt was made in most studies to use appropriate statistical techniques to control for between-group differences in either baseline characteristics or duration of follow-up.

Attrition of the sample also appeared to be a common concern across studies, from small single-center evaluations to large registry studies. Even the widely-cited Swedish Obese Subjects (SOS) study, a matched prospective examination of bariatric surgery and nonsurgical management, saw a precipitous drop-off in patient availability after two years of follow-up (Sjöström, 2013; Sjöström, 2014). (Note: this study is not included in our primary analysis because over two-thirds of patients received gastroplasty, a procedure no longer performed in the U.S.) Large-scale patient attrition is certainly understandable in these patients, given the clinical and mental complexity involved in obesity-related illness and the attendant difficulties for patients in adhering to post-procedure follow-up programs; however, very few studies accounted for patient attrition using well-accepted methods such as survival analysis and/or actuarial reporting. In all other studies, concerns with observing long-term results only in a small percentage still adherent to the program are of critical importance, as the censoring is "informed"— those not receiving long-term benefits of bariatric surgery are more likely to be lost to follow-up.

Finally, most studies were lacking standardized definitions for important outcomes. For example, relatively few studies used an accepted classification system (e.g., Clavien) for categorizing the severity of procedure-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 type 2 diabetes was determined based on reductions of 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.

We identified 35 reports from 30 randomized controlled trials of bariatric surgery, four of which were rated to be of poor quality. Poor ratings for RCTs were a result of ineffectual randomization (e.g., BMI differences of >3 points, no control for these differences in analysis) and/or systematic differences in follow-up between groups (e.g., a surgical group studied for six weeks, a nonsurgical group evaluated over six months). Summary statistics for the good- and fair-quality RCTs are provided in **Table ES-1** on the following page, organized by type of comparison made. As shown in the table, not all studies reported on key outcomes of interest other than weight changes, such as resolution of comorbidities and procedure-related harms.

Of the remaining studies, 59 (34%) were prospective and 85 (59%) were retrospective cohort comparisons. Somewhat surprisingly, study quality was of essentially equivalent concern for both prospective and retrospective studies. A total of 29 of 59 (49%) prospective studies were rated poor quality, while 46 of 85 (54%) retrospective studies were rated poor. Reasons for a poor-quality rating were similar to those for RCTs—imbalanced treatment groups, differential follow-up and/or high patient attrition, and lack of use of statistical techniques to control for between-group differences.

Table ES-1: Available good- and fair-quality randomized controlled trials of bariatric surgery, by type of comparison

Comparison	# Studies* / # patients	Range of follow-up, months (median)	Measures (studies reporting)
Surgery vs. nonsurgical mgmt.	13 / 1,007	12-120 (24)	Weight (13) Comorbidity resolution (8) Harms (8)
RYGB vs. VSG	7 / 725	1-36 (12)	Weight (6) Comorbidity resolution (4) Harms (4)
RYGB vs. LAGB	2 / 248	50-120 (85)	Weight (2) Comorbidity resolution (1) Harms (2)
RYGB vs. BPD/DS	3 / 137	24-60 (48)	Weight (3) Comorbidity resolution (2) Harms (2)
Other surgical comparisons	1 / 80	36	Weight (1) Comorbidity resolution (0) Harms (1)

*31 reports of 26 distinct RCTs

RYGB: Roux-en-y gastric bypass; VSG: vertical sleeve gastrectomy; LAGB: laparoscopic adjustable gastric banding; BPD/DS: biliopancreatic diversion with duodenal switch

A summary evidence table (**Table ES-2**) capturing the strength of evidence for each of the six key questions of interest can be found on the following page. As described at the beginning of this section, lack of long-term comparative data on mortality and other important clinical outcomes limits the conclusions that can be drawn to those based on more intermediate endpoints such as weight loss, shorter-term comorbidity resolution, and procedure-related harms. A detailed assessment of the evidence for each key question is presented in the sections that follow.

Table ES-2: Summary evidence table: Bariatric surgery, compared to nonsurgical management, and by procedure in adult and pediatric populations

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
KQ1a: Effectiveness of Bariatric Surgery in Adults								
Surgery N=2,083 RCT=14	Nonsurg Mgmt	Medium	Consistent	Direct	Precise	+++ Moderate	*Incremental* Mean reduction in BMI: 7.4 Likelihood of T2DM resolution: log OR 3.6	Benefits also seen with BMI 30-34.9, primarily with T2D resolution
VSG N=1,461 RCT=6	RYGB	Medium	Consistent	Direct	Precise	+++ Moderate	*Comparable* No significant BMI differences	Limited data on comorbidity resolution
LAGB N=3,111 RCT=2	RYGB	Medium	Consistent	Direct	Precise	+++ Moderate	*Inferior* >BMI change and EWL for RYGB	Evidence mixed for comorbidity resolution
BPD/DS N=216 RCT=3	RYGB	Medium	Consistent	Direct	Precise	+++ Moderate	*Incremental* Reduction in BMI of 6-7 pts for BPD	Limited data on comorbidity resolution
KQ1b: Effectiveness of Bariatric Surgery in Pediatric Populations								
Adolescents Surgery N=50 RCT=1	Nonsurg Mgmt	Medium	N/A	Direct	Imprecise	++ Low	*Incremental* Mean reduction in BMI: 9.6	Complete resolution of metabolic syndrome in surgical arm
	RYGB	*NO STUDIES*						

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
LAGB N=890 RCT=0	RYGB	High	N/A	Direct	Imprecise	+ Insufficient		Groups differed significantly at baseline; no differences after adjustment
BPD/DS	RYGB	*NO STUDIES*						
Children (<12)		*NO STUDIES*						
KQ2: Components of Bariatric Surgery Management Correlated with Treatment Success								
Surgery	By procedure and vs. nonsurgical mgmt	High	Inconsistent	Indirect	Imprecise	+ Insufficient		Limited evidence suggesting correlation with: *Post-procedure support groups *Team care including dietician *Psychosocial stability
KQ3: Potential Harms of Bariatric Surgery								
Peri-operative Mortality	Total of 32 studies reporting harms (N=31,637)	High	Inconsistent	Indirect	Imprecise	+ Insufficient		Underreported (75 deaths in 32 studies)

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
Overall Complications		High	Inconsistent	Direct	Imprecise	++ Low	Median by proc: RYGB: 19.4 VSG: 9.5 LAGB: 17.9 BPD: 31.6	Inconsistent reporting and categorization of complications; RCTs underpowered to detect differences
Reoperation		High	Inconsistent	Direct	Imprecise	++ Low	Median by proc: RYGB: 6.0 VSG: 2.0 LAGB: 14.8 BPD: 13.0	Inconsistent reporting and categorization of reoperations; RCTs underpowered to detect differences
KQ4: Differential Effectiveness and Safety According to Health-System or Program Factors								
Surgeon Experience	N/A	High	Consistent	Direct	Imprecise	++ Low	Improvement in outcomes after 68-250 cases	Variable estimates by study and procedure
Procedure Volume	N/A	Medium	Consistent	Direct	Imprecise	++ Low	Lower complication rates, better weight loss at surgeon or hospital volume >50-200 cases	Variable estimates by study and procedure

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
Certification/ Accreditation	Non-COE facilities	High	Inconsistent	Indirect	Imprecise	++ Low	Mixed evidence of benefit at COE vs. non-COE facilities	One comparative study, other posttest evaluations after Medicare NCD
Core Team Members	Surgical team only	High	Inconsistent	Indirect	Imprecise	++ Low	Some data suggest multidisciplinary care superior to surgical team only	Confounded by COE requirements that bariatric care be multi-disciplinary
Pre/Post-Procedure Support	Multiple	Medium	Inconsistent	Direct	Imprecise	++ Low	No effect of pre-operative weight loss or dietary counseling; post-operative dietary counseling and support more effective	Problematic to compare variable approaches across studies
KQ 5: Differential Effectiveness and Safety According to Patient Factors								
Demographics	N/A	Medium	Inconsistent	Direct	Imprecise	++ Low	No consistent effects of age, gender, or race	
BMI	N/A	High	Consistent	Direct	Imprecise	++ Low	Best outcomes for BMI ≥40 vs. 30-39 and 50+	Comparison across studies due to limited subgroup data

Study Information	Comparators	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect	Comments
Comorbidities/ Prior Events	N/A	High	Inconsistent	Indirect	Imprecise	++ Low	Cardiac comorbidities affect RYGB outcomes more than LAGB	
Smoking Status	*NO STUDIES*							
Psychosocial Health	*NO STUDIES*							
Program Adherence	N/A	High	Inconsistent	Indirect	Imprecise	+ Insufficient	EWL lower in LAGB with poor pre-op program adherence; no effect for RYGB	Single retrospective cohort
KQ 6: Costs and Cost-Effectiveness of Bariatric Surgery								
Surgery	Nonsurg Mgmt	Medium	Consistent	Indirect	Imprecise	+++ Moderate	$2,000-$30,000 per QALY	Variable data sources and assumptions
VSG	RYGB	Medium	Inconsistent	Indirect	Imprecise	++ Low	Less expensive but slightly less effective	Data only from ICER model
LAGB	RYGB	Medium	Consistent	Indirect	Imprecise	+++ Moderate	Less expensive and less effective	Variable data sources and assumptions
BPD/DS	RYGB	Medium	Inconsistent	Indirect	Imprecise	++ Low	$65,000-$97,000 per QALY	Data only from ICER model

BMI = Body Mass Index; BPD/DS = Biliopancreatic Diversion/Duodenal Switch; COE = Centers of Excellence; EWL = Excess Weight Loss; f/u = follow-up; ICER = Institute for Clinical and Economic Review; LAGB = Laparoscopic Adjustable Gastric Banding; OR = Odds Ratio; QALY = Quality-Adjusted Life Year; RCT = Randomized Controlled Trial; RYGB = Roux-en-Y Gastric Bypass; VSG = Vertical Sleeve Gastrectomy

Key Question #1a: What is the comparative clinical effectiveness of bariatric surgery procedures versus conventional weight-loss management in adults (i.e., age 21 and older)?

Across a range of procedures, study designs, and duration of follow-up, bariatric surgery results in greater sustained weight loss and resolution of comorbidities (primarily type 2 diabetes) than nonsurgical interventions. These results are challenged by a lack of good-quality long-term data on durability of benefit. Long-term data that are available suggest that weight recidivism and comorbidity relapse are not uncommon, although more data are needed. Among types of bariatric procedures commonly performed in the U.S., biliopancreatic diversion with or without duodenal switch appears to produce the best outcomes, followed by gastric bypass, sleeve gastrectomy, and gastric banding. Evidence is insufficient to determine the comparative impact of any of these procedures or of nonsurgical care on long-term all-cause or cause-specific mortality.

The evidence comparing bariatric surgical procedures to conventional weight-loss management in adult patients is summarized below by key outcome of interest. For completeness, head-to-head comparisons of each type of bariatric procedure are also summarized as part of this key question. 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). Note that more detailed discussions of outcomes other than mortality, weight loss, and comorbidity resolution are available in the full report, as are summaries of retrospective comparative cohort studies.

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 noted major limitations 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). As noted previously, we did not include the SOS study in our analytic set because the primary surgical intervention was gastroplasty, which is no longer performed in the U.S. 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 large cohort 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), and 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 Veterans Affairs 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. However, a more recent VA-based evaluation examined all-cause mortality at multiple timepoints during 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 1-5 years, however, surgical patients experienced significantly lower rates of mortality (HR: 0.45; 95% CI: 0.36, 0.56); findings were similar at 5-14 years of follow-up.

Bariatric Surgery vs. Nonsurgical Management

We identified a total of 21 reports of good- or fair-quality RCTs (14) and prospective cohort studies (7) comparing one or multiple forms of bariatric surgery to nonsurgical management. Characteristics of included studies can be found in Appendix B. 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 type 2 diabetes (Courcolas, 2014; Dixon, 2008; Halperin, 2014; Ikramuddin, 2013; Leonetti, 2012; Liang, 2013; Mingrone, 2012; Schauer 2012, 2014; Scopinaro, 2011).

Impact of Bariatric Surgery 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 ES-6 on the following 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 (I^2=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.

Noticeably missing from weight-change data is any analysis of long-term weight regain following surgery. The Swedish Obese Subjects (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 ten 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 U.S.). 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 kilograms 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.

Figure ES-6: Meta-analysis of mean BMI at study end: bariatric surgery vs. nonsurgical management
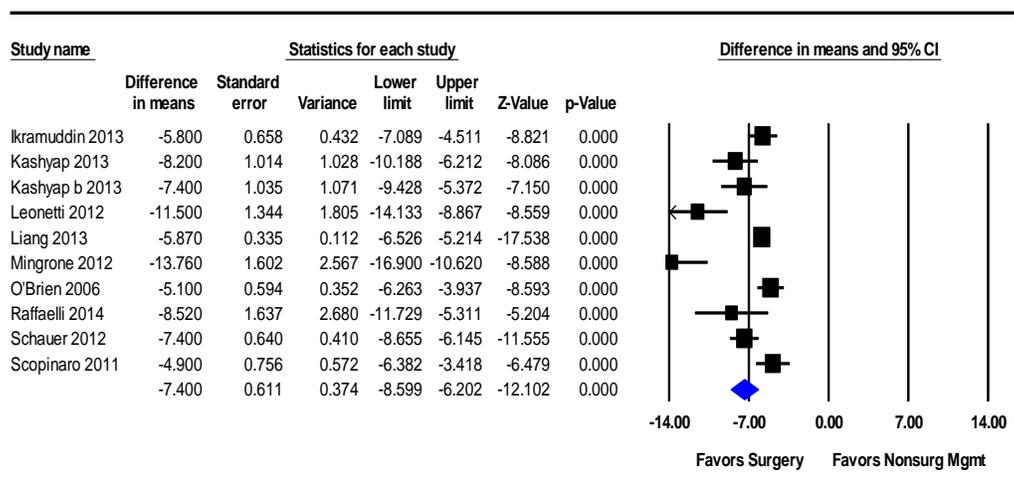
Study name	Statistics for each study							Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Ikramuddin 2013	-5.800	0.658	0.432	-7.089	-4.511	-8.821	0.000	
Kashyap 2013	-8.200	1.014	1.028	-10.188	-6.212	-8.086	0.000	
Kashyap b 2013	-7.400	1.035	1.071	-9.428	-5.372	-7.150	0.000	
Leonetti 2012	-11.500	1.344	1.805	-14.133	-8.867	-8.559	0.000	
Liang 2013	-5.870	0.335	0.112	-6.526	-5.214	-17.538	0.000	
Mingrone 2012	-13.760	1.602	2.567	-16.900	-10.620	-8.588	0.000	
O'Brien 2006	-5.100	0.594	0.352	-6.263	-3.937	-8.593	0.000	
Raffaelli 2014	-8.520	1.637	2.680	-11.729	-5.311	-5.204	0.000	
Schauer 2012	-7.400	0.640	0.410	-8.655	-6.145	-11.555	0.000	
Scopinaro 2011	-4.900	0.756	0.572	-6.382	-3.418	-6.479	0.000	
	-7.400	0.611	0.374	-8.599	-6.202	-12.102	0.000	

Heterogeneity: Tau^2= 2.81; Q=55.8; df=9; I^2=84%

Test for overall effect: Z=-12.1 (p<0.001)

Impact of Bariatric Surgery 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 type 2 diabetes. **Figure ES-7** on the following page shows the results of our meta-analysis of resolution of type 2 diabetes 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 odds ratio [OR] 3.62; 95% CI 2.49, 4.74).

Although the results of the SOS study were not included in our meta-analysis, long-term data on diabetes remission are available. While 72% of surgery patients with type 2 diabetes 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 type 2 diabetes, however (96%, 84%, and 78% after two, 10, and 15 years, respectively) (Sjöström, 2012).

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 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 vs. 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 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%) vs. resolution in 7 of 15 (46.7%) (p<0.002 for the comparison). Similar patterns were observed in a ten-year follow-up from this study, although nearly half of those originally randomized to nonsurgical management crossed over to LAGB surgery (O'Brien, 2013).

Figure ES-7: Meta-analysis of resolution of type 2 diabetes: 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)

As with weight changes, degradation in performance of bariatric surgery with respect to comorbidity resolution was rarely evaluated in available RCTs. One RCT evaluated the performance of 150 patients with type 2 diabetes (mean age 48.5 years, 66% female, mean BMI 36) who were randomized to receive

intensive medical therapy alone (lifestyle counseling, weight management, home glucose monitoring, and optimized use of antidiabetic medications), medical therapy + RYGB, or medical therapy + VSG and were followed for 12 months (Schauer, 2012). Achievement of HBA1c levels <6% was observed 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). Over 90% of the original sample was available for 3-year follow-up (Schauer, 2014); achievement of HbA1c <6% was reduced over this timeframe, but remained substantially higher in the surgical groups (38%, 24%, and 5% for RYGB, VSG, and medical therapy, respectively, p≤0.01 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).

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, defined as 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 type 2 diabetes 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 defined; 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.

Gastric Bypass vs. Sleeve Gastrectomy

We identified a total of six RCTs and six prospective comparative cohort studies that met our criteria for good or fair quality, involved comparisons of RYGB to VSG, and had at least 12 months of follow-up. An additional RCT described previously compared both RYGB and VSG to nonsurgical management (Schauer, 2012). Characteristics of these studies and main results can be found in Appendix B.

Impact on Measures of Body Weight

Across all seven RCTs of interest (Kehagias, 2011; Paluszkiewics, 2012; Peterli, 2012; Peterli, 2013; Ramon, 2012; Schauer, 2012; Vix, 2013), reductions in BMI (11-15 points on average, irrespective of baseline values) and other measures of body weight change from baseline were substantial for both RYGB and VSG, but did not differ statistically in _any_ of these studies. We conducted a meta-analysis of mean BMI at study end among those RCTs reporting these values along with appropriate measures of variance and drew similar conclusions (mean difference 0.30, 95% CI -0.83, 1.42) (see **Figure ES-8** below). Similarly, no statistical differences were observed in any of the prospective cohort studies. One cohort of 136 patients (mean age 42, 72% female, mean BMI 45) reported a percentage of excess BMI loss of 76% for RYGB at 2 years vs. 63% for VSG, but this difference was not tested statistically (Gehrer, 2010).

Figure ES-8: Meta-analysis of mean BMI at study end: RYGB vs. VSG

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Kehegias 2011	1.700	1.033	1.067	-0.325	3.725	1.646	0.100
Paluszkiewicz 2012	1.000	1.297	1.681	-1.541	3.541	0.771	0.441
Peterli 2012	-0.800	1.470	2.160	-3.681	2.081	-0.544	0.586
Schauer 2012	-0.400	0.674	0.454	-1.721	0.921	-0.594	0.553
	0.296	0.574	0.329	-0.828	1.421	0.517	0.605

Difference in means and 95% CI. Scale: -14.00, -7.00, 0.00, 7.00, 14.00. Favors RYGB — Favors VSG

Heterogeneity: Tau^2= 0.28; Q=3.7; df=3; I^2=20%

Test for overall effect: Z=0.52 (p=0.605)

Impact on Resolution of Comorbidities

Resolution of comorbidities was assessed as a binary variable in a total of four studies comparing RYGB to VSG (Benaiges, 2011; Benaiges, 2013; Paluzkiewicz, 2012; Peterli, 2013). Heterogeneity in study designs and patient populations precluded meta-analysis of these studies. As with body weight measures, comorbidity resolution was substantial for both types of surgery and did not statistically differ between groups for nearly all comparisons. In a cohort comparison of 140 patients (mean age 45, 82% female, mean BMI 46) who were followed for 12 months (Benaiges, 2011), resolution of hypertension did not differ between groups, but resolution of hyperlipidemia did (100% vs. 75% for RYGB and VSG respectively, p=0.014). An RCT of 217 patients (mean age 43, 72% female, mean BMI 44) (Peterli, 2013) found no statistical differences in one-year resolution of hypertension, dyslipidemia, diabetes, sleep apnea, back or joint pain, hyperuricemia (excess uric acid in blood), or depression between groups. A statistical difference was noted for resolution of gastroesophageal reflux disease (GERD), however (23% vs. 14% for RYGB vs. VSG, p=0.008).

Gastric Bypass vs. Gastric Banding

We identified three RCT reports and four prospective comparative cohort studies of good- or fair-quality that evaluated outcomes for RYGB and LAGB over a minimum of 12 months of follow-up. Details of each study and main results can be found in Appendix B. Of note, two of the RCT reports related to five- and 10-year follow-up from a single RCT (Angrisani 2007; Angrisani 2013). Differences in study design and the outcomes measured precluded formal meta-analysis of outcomes in this comparison set; study findings are nonetheless summarized descriptively below.

Impact on Measures of Body Weight

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 excess weight loss 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). Excess weight loss remained in favor of RYGB (69% vs. 46% for LAGB, p=0.03).

The other RCT was a fair-quality evaluation of 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. Excess weight loss 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% excess weight loss, occurred in 17% of LAGB patients and zero RYGB patients (not statistically tested).

Similar findings were observed in the five prospective cohort comparisons (Bowne, 2006; Cottam, 2006; Puzziferri, 2008; Weber, 2004). The largest of these examined 1,733 individuals (1,102 and 631 for RYGB and LAGB respectively) (mean age 44, 85% female, mean BMI 50) at a single large institution, and followed patients for two years (Puzziferri, 2008). Excess weight loss was statistically-significantly greater for RYGB at two years (75% vs. 44% for LAGB, p<0.0001), and RYGB patients achieved >40% excess weight loss more quickly than their LAGB counterparts.

Impact on Resolution of Comorbidities

Resolution of comorbidities was assessed in binary fashion in one of the RCTs and three cohort studies. Five-year data from the Angrisani RCT (Angrisani, 2007) indicated that diabetes, hyperlipidemia, and sleep apnea had resolved in the four patients with these conditions at baseline, regardless of surgical assignment. The only measured comorbidity that remained unresolved was hypertension in three LAGB patients at baseline.

Results were somewhat mixed in the cohort studies. In an evaluation of 106 individuals (mean age 43, 80% female, mean BMI 56) followed for a median of 16 months (Bowne, 2006), RYGB was associated with significantly greater resolution of sleep apnea (88% vs. 39%, p=0.01), but no statistical differences in resolution of diabetes, hypertension, dyslipidemia, asthma, or arthritis. In contrast, a matched evaluation of 362 patients (mean age 43, 84% female, mean BMI 47) followed for up to three years found statistically greater levels of resolution of diabetes, hyperlipidemia, and hypertension among

those receiving RYGB (Cottam, 2006). Finally, another matched comparison of 206 patients (mean age 40, 79% female, mean BMI 48) showed statistically greater resolution of type 2 diabetes and dyslipidemia among RYGB patients, but no statistical difference in hypertension.

Gastric Bypass vs. Biliopancreatic Diversion (With or Without Duodenal Switch)

We identified five reports on three RCTs (Hedberg, 2012; Olsen, 2012; Risstad, 2015; Søvik, 2010 and 2011) and one prospective cohort study (Nanni, 2012) directly comparing RYGB with BPD, with or without DS, of good- or fair-quality, and with follow-up of at least 12 months. Details of each study and major findings are provided in Appendix B.

Impact on Measures of Body Weight

In the three available RCTs, there was consistent and statistically-significantly greater reductions in measures of body weight with BPD/DS relative to RYGB, with mean reductions of 6-8.5 BMI points in all three studies. Unfortunately, appropriate measures of variance were available in only two of these RCTs, so meta-analyses were not conducted. Findings were similar for the prospective cohort study (Nanni, 2012), but could not be included in a meta-analysis because of a lack of hypothesis testing of body-weight measures.

The durability of procedure performance was examined in the three reports of the Søvik RCT. In the 2010 Søvik study, 60 super-obese patients (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). Significant differences in body weight and excess BMI lost were noted in both reports. 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).

Impact on Resolution of Comorbidities

Information on resolution of comorbidities in this comparison set was extremely limited. In an RCT of 47 super-obese patients (mean age 39, 47% female, mean BMI 54) who were followed for up to four years (Hedberg, 2012), the percentage of patients achieving an HbA1c level <5% was reported to be 100% in the BPD/DS group vs. 82% in the RYGB group, although this was not statistically tested. In another small RCT of 30 super-obese patients (mean age 35, 67% female, mean BMI 55) who were followed for two years (Olsen, 2012), the presence of sleep apnea was self-reported by one patient in the BPD/DS group, but this was not tested statistically, nor was it compared to baseline prevalence. Long-term follow-up of the Søvik study in the super-obese (see above) yielded no statistically-significant differences in remission of type 2 diabetes or metabolic syndrome (Risstad, 2015).

Key Question #1b: What is the comparative clinical effectiveness of bariatric surgery procedures versus conventional weight-loss management in children (age <21), on an overall basis and by specific age groups (i.e., 18-20, 13-17, 12 or less)?

There is a lack of both short- and long-term data demonstrating effectiveness for any bariatric surgery procedure in both children and adolescents. We found only two studies of sufficient quality: one RCT (O'Brien, 2010) which compared LAGB to conventional weight-loss treatment, and one retrospective

cohort (Messiah, 2013) comparing LAGB to RYGB. Six additional comparative cohorts were identified but these studies were determined to be of poor quality; one of these studies is described in detail below because of its large sample size (see Appendix B for information on poor quality studies). Only one case series (Silberhumer, 2011) evaluating the long-term effects of LAGB in adolescents met our criteria for inclusion. There were no comparative studies evaluating any bariatric procedure exclusively in children (under 13 years) or the use of BPD in any patient under 21 years old.

We identified a single 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 29.6kg/m² in the surgical cohort and 39.2kg/m² in the lifestyle intervention group, representing a significantly greater percentage of excess weight loss 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.

Despite being of generally good quality, this study has some important limitations. First, although the authors used recruitment measures to minimize bias to treatment, these results may reflect the subset of patients who had access to surgical intervention without barriers to insurance coverage. In addition, while the study was powered to report on changes in weight, the authors were limited by the small sample size in assessing statistical differences between groups for other health-related outcomes, including adverse events. Finally, because of the relatively short duration of the study (2 years), the authors could not comment on the long-term benefits of surgery.

Of the five comparative cohort studies we identified in our literature 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 timepoint, patients in both groups had significant weight loss and significant improvement of comorbidities, including diabetes, 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.

There are some methodological concerns with this study beyond its retrospective design. As with other comparative studies on bariatric surgery, long-term safety and efficacy data are absent. The authors also note that the data entry into BOLD is performed by participating surgeons and may underrepresent true rates of complications. There is also a concern with missing follow-up data for all bariatric outcomes – an issue that is even more prevalent in an older adolescent population who are more mobile than in adults – which may have introduced selection bias. Nevertheless, the authors tested for

potential differences between groups with and without complete follow-up data and found no differences.

Of the six poor-quality comparative cohorts, one retrospective study (Lennerz, 2014) involved 345 patients (mean age 19, 67% female, mean BMI 47.4) between 8-21 years who received either RYGB, LAGB, or VSG over one and a half years of follow-up. Patients in the RYGB group had the largest reduction in BMI compared to either VSG or LAGB (-32.9%, -29.4%, -20.0% for RYGB, VSG, and LAGB, respectively, p<0.001), and there were no statistical differences for weight loss outcomes between patients <18 and 18-21 years old. Prevalence of comorbidities also decreased, including diabetes, hypertension and sleep apnea; these data are not reported by procedure, however. Although this was the largest of the poor-quality comparative studies, there are serious quality concerns, including unmatched groups at baseline and a high attrition rate with only 48% of the original population available for follow-up.

In order to assess long-term outcomes of bariatric surgery in an adolescent population, we also 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 our criteria for inclusion. 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 5 years, with only 10% lost to follow-up, the mean BMI was 27.3 kg/m², representing a mean excess weight loss of 92.6%, and the difference between timepoints was significant up to 3 years (p<0.01). All patients with a functional band had 100% resolution of all comorbidities, and quality of life after surgery continued to improve over time with significant differences between all points of follow-up up to five years (p=0.01).

We identified four additional case series with 217 patients that met our inclusion criteria for sample size and mean duration of follow-up – three evaluating the use of VSG and one evaluating LAGB – for a total of 267 patients across all studies. However, none of these studies maintained at least 80% enrollment throughout follow-up duration. Mean age ranged from 15.8 to 19.5 years old, and excess weight loss ranged from 61.1% to 101.6%. Mortality was either not reported or no deaths occurred. Details on all the case series relevant to our analysis are represented in **Table ES-3** on the following page.

Table ES-3: Case series with >2 years of follow-up in children/adolescents undergoing bariatric surgery

Study	Boza 2012	Nadler 2008	Nocca 2014	Raziel 2014	Silberhumer 2011
Procedure	VSG	LAGB	VSG	VSG	LAGB
# patients @ baseline	51	73	61	32	50
Mean age/BMI	18.0/38.5	15.8/48	19.5/45.7	16.8/43.2	17.1/45.2
%EWL @ study end	92.9	61.0	78.4	101.6	92.6
Mean f/u	2 years	2 years	2 years	60 months	86 months
Max point with 80% f/u	1 year	<6 months	6 months	3 months	5 years
# patients with 80% f/u	34	16	5	2	45
Reoperations	1	11	1	2	6

BPD = Biliopancreatic Diversion; LAGB = Laparoscopic Adjustable Gastric Banding; RYGB = Roux-en-Y Gastric Bypass; VSG = Vertical Sleeve Gastrectomy; %EWL = percentage of Excess Weight Loss; f/u = follow-up, BMI = Body Mass Index

In order to understand whether our selection criteria eliminated valuable case series data in certain subgroups of pediatric patients, we evaluated data from a recently published systematic review that used less restrictive criteria (i.e., 10 or more patients, no restrictions on follow-up) (Black, 2013). Even with these relaxed criteria, a total of only 637 patients were evaluated across 23 included studies, only two of which allowed children under 12. A meta-analysis of change in BMI from baseline in these studies suggested a substantial reduction (weighted mean difference: -13.5; 95% CI: -15.1, -11.9), but when stratified by procedure, data were only considered sufficiently robust for RYGB (results were highly variable with LAGB, and there were too few studies of VSG or BPD/DS). Data on resolution of comorbidities and complications were not included in all studies, and reporting methods were not consistent enough to allow for meta-analysis of these data.

Key Question #2: What components of the management of patients undergoing bariatric surgery (e.g., selection of candidates for surgery, multi-disciplinary care team, pre- and/or post-procedure counseling and support) appear to be correlated with higher levels of "treatment success" (e.g., sustained weight loss, reduction in comorbidity burden, etc.)?

Several patient characteristics and programmatic factors have been associated with higher levels of treatment success. Younger patients and those with lower pre-operative BMIs achieve greater excess weight loss after surgery. There is not a consistent correlation between comorbidity status and weight loss, although type 2 diabetes status has been found to have an inverse relationship with weight loss. Multi-disciplinary care, consistent follow-up, and post-operative counseling appear to be essential to producing better outcomes. Patient motivation is also an important factor in achieving successful weight loss. Low surgeon or hospital volume is associated with greater mortality and complications, as are older age and male gender.

Several components of the management of patients undergoing bariatric surgery have been found to be correlated with higher levels of treatment success. Both programmatic factors and certain candidate characteristics have been attributed with a higher likelihood of greater and sustained weight loss.

Programmatic factors are discussed more extensively in Key Question 4. The key factors of each of the studies reviewed for this question are summarized in Appendix C, and described in further detail in the sections that follow.

Selection of Candidates

Certain patient characteristics make eligible candidates more or less likely to have success in bariatric surgery. As discussed in further detail in Key Question 5, studies have had inconsistent findings in relation to gender and weight loss: depending on the statistic reported (i.e., BMI change, kilograms lost, excess weight loss [EWL]), some studies report EWL to be greater in females (Melton, 2008; Bueter, 2007; Dallal, 2009; Chen, 2012; Carlin, 2013), greater in males (Dallal, 2009; Compher, 2012; Messiah, 2013; Ma, 2006; Sarwer, 2008), or without statistical differences (Lutfi, 2006; Ortega, 2012; Perugini, 2003).

Age and baseline BMI have been consistently reported to be negatively associated with EWL, with heavier and older patients losing a lower percentage of weight (Ortega, 2012; Carlin, 2013; Chevallier, 2007; Ma, 2006; Still, 2014). For example, a matched cohort study of 8,847 patients (mean age 46, 74% female, mean BMI 48 kg/m^2) found that EWL was 5.7%, 8.1%, and 13.5% lower for patients 60 years of age or older after 12 months follow-up, compared to patients under 30 years of age for RYGB, VSG, and LAGB, respectively (Carlin, 2013).

A number of studies have shown an inverse correlation between diabetes status and weight loss success: having type 2 diabetes is associated with less weight loss after surgery (Melton, 2008; Wittgrove, 2000; Ma, 2006; Perugini, 2003; Ortega, 2012; Still, 2014). In an analysis of weight data from 555 RYGB patients, Melton et al. reported that type 2 diabetes patients had an odds of suboptimal weight loss, which they defined as <40% EWL, of 2.6 (95% CI: 1.5, 4.8) (Melton, 2008). Other comorbidities such as depression and binge eating disorder have _not_ shown a correlation with weight loss (Ma, 2006).

Whereas weight loss outcomes have been inconsistent in relation to gender, mortality and complication findings have not: several studies have found male gender to be associated with greater mortality, longer length of hospital stay, and higher rates of complications (Masoomi, 2011; Nguyen GC, 2013; Nguyen, 2011; Padwal, 2013).

Several other patient characteristics are associated with greater mortality, including race, and older age (Masoomi, 2011; Nguyen, 2013; Nguyen, 2011; Padwal, 2013). Comorbidity status at baseline is associated with greater complication rates (Masoomi, 2011; Perugini, 2003; Padwal, 2013; Ortega, 2012) although evidence of mortality in relation to obesity-related comorbidities such as hypertension and type 2 diabetes has been inconsistent.

Psychiatric comorbidity also may adversely affect patient selection. Although adequate perioperative counselling is suggested to improve the results of surgery, patients with social phobia and avoidant personality disorders are less willing to participate (Lier, 2011). In a study of 363 patients eligible for RYGB or VSG, Sockalingam et al. (2013) showed that eligible bariatric surgery candidates who did not follow through with surgery had significantly higher rates of overall past Axis I psychiatric disorders than patients who completed surgery (58.1 vs. 46.6 %, p=0.035), past anxiety disorders (17.4 vs. 9.4 %, p=0.03), and past substance use disorders (8.7 vs. 3.7 %, p=0.03).

Programmatic Factors

In addition to age, baseline BMI, and diabetes status, a few key programmatic factors have been associated with surgical success. First, a multidisciplinary care approach has become a common element of bariatric surgery, both before and after the procedure. We found only a single study that compared outcomes between patients who receive 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/m2) were followed for up to 12 months. At 12 months, 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 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.

Not surprisingly, program adherence after surgery has 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 calculated that the odds of $\geq$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 (1.4-5.7). Correspondingly, adherence to scheduled follow-up visits and compliance with recommended post-operative care, predict a greater decrease in BMI during the first 4 years after LAGB[1] (Pontiroli, 2007).

As discussed in further detail in Key Question 4, participation in post-operative support groups has been associated with better weight outcomes (Nijamkin, 2012; Nijamkin, 2013, Elakkary, 2006). However it is uncertain whether dietary counseling following surgery improves outcomes. While there have been many studies assessing the effectiveness of _pre-operative_ dietary counselling and weight loss programs (Carlin, 2008; Harnisch, 2008; Huerta, 2008; Jamal, 2006; Becouarn, 2010; Van Nieuwenhove, 2011; Parikh, 2012; Alami, 2007), we found only one study that analyzed post-operative dietary counseling (Sarwer, 2012). In this study, 84 patients (mean age 42, 63% female, mean BMI 52 kg/m2) undergoing RYGB or LAGB were randomized to receive either dietary counseling or standard postoperative care for the first four months after surgery (Sarwer, 2012). The participants completed measures of macronutrient intake and eating behavior at baseline and 2, 4, 6, 12, 18, and 24 months after surgery. While the patients who received dietary counseling achieved greater numeric weight loss than those who received standard care, the difference did not reach statistical significance. Similarly, while dietary counseling patients consumed fewer calories (1,170 vs. 1,463), more protein (10% of daily intake vs. 13%) and less sweets (46% of daily intake vs. 50%) than patients who were not counseled, these differences did not reach statistical significance (Sarwer, 2012).

Psychosocial Factors

Certain psychosocial factors may also impact levels of surgical success. Weineland and colleagues randomized 39 bariatric patients who underwent either sleeve gastrectomy or gastric bypass surgery

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

(mean age 43, 90% female, mean BMI 37 kg/m2) to two post-operative approaches: (1) acceptance and commitment therapy (ACT), including two face-to-face sessions and support via an Internet application; or (2) treatment as usual (TAU) comprising the standard follow-up used by the surgical team. Participants in the ACT condition significantly improved on subjective binge eating ($F(1,37) = 8.38$, $p = 0.006$, effect size $\eta^2_p=0.19$), body dissatisfaction ($F(1,37) = 5.65$, $p = 0.023$, effect size $\eta^2_p=0.13$) , quality of life ($F(1,37) = 7.65$, $p = 0.022$, effect size $\eta^2_p=0.13$) and acceptance of weight related thoughts and feelings ($F(1,37) = 8.59$ $p = 0.006$, effect size $\eta^2_p=0.18$), as compared to those in the TAU group (Weineland, 2012).

Support groups and counseling can help patients modify their lifestyles, adhere to care guidelines, and have better overall outcomes. Those who participate in post-operative support groups have had better weight loss outcomes than those who do not (Orth, 2008a; Weineland, 2012). Orth et al. (2008a), for example, found that RYGB patients who attend support groups have a significantly greater decrease in BMI than patients who do not attend such groups (42% vs. 32%; p<0.03).

With the exception of pre-surgical weight loss requirements (discussed in further detail in Key Question 4), few studies have analyzed pre-operative interventions. We found two studies that looked at pre-surgical counseling (Lier, 2012; Leahey, 2009). Interestingly, these studies found that patients had poorer attendance at pre-operative counseling sessions and did not have significantly different weight loss from patients who did not participate in any sessions. For example, in an RCT of 141 patients (mean age 42, 73% female, mean BMI 45.2 kg/m2) undergoing gastric bypass surgery, patients were randomized to receive psychological group counseling before surgery or "treatment as usual" (Lier, 2012). After one year of follow-up, the groups showed no statistical differences regarding weight loss or adherence to lifestyle changes in diet and physical activity. Another prospective study compared 32 pre-operative and post-operative LAGB and RYGB patients (mean age 49, 78% female, mean BMI 44 kg/m2) who had been referred to a 10-week intervention designed to reduce eating behaviors associated with postoperative weight gain (e.g., loss of control while eating, grazing) (Leahey, 2009). Compared to post-surgical patients, pre-surgical patients attended fewer sessions ($t(18)=2.51$, $p=0.02$) and were less likely to complete the intervention (14% pre-surgical completers vs. 91% post-surgical completers, p=0.007) (Leahey, 2009).

Self-selecting to attend meetings or adhere to care recommendations may be the result of other intrinsic patient characteristics, such as discipline or motivation, which make patients more likely to have weight loss success and adhere to post-operative care recommendations (Ray, 2003). In an analysis of data from 149 RYGB patients (mean age 29, 81% female, mean BMI 52 kg/m2) operated on by the same surgeon, Ray and colleagues found that patients who perceived "moderate to severe obesity-related health problems" in themselves lost a greater percentage of excess weight loss than those who did not perceive such problems in themselves (59% vs. 43%, p<0.05). Moreover, those who reported that their motivation for seeking weight loss surgery was not from an extrinsic pressure (such as social distress from obesity) but rather an intrinsic drive to lose weight, were also more successful (62% vs. 53%, p<0.05) (Ray, 2003).

In addition to predicting weight loss success, several studies have analyzed factors predictive of mortality and complications. As discussed in more detail in Key Question 4, hospitals and surgeons with lower case volume tend to have higher rates of complications and mortality (Birkmeyer, 2010; Gould, 2011; Courcoulas, 2003; Nguyen, 2004; Murr, 2007; Perugini, 2003; Smith, 2013; Weller, 2007). Murr et al. (2007) used a multiple variable binary logistic regression model adjusting for patient age, gender, and procedure calendar year and found a significant association between surgeon's procedure volume and

the odds of developing an in-hospital complication: patients who underwent a procedure from a surgeon who had performed 1-5 procedures in the five years of the study (relative to a patient whose surgeon had undertaken ≥500 procedures) had an odds of developing a complication of 2.0 (95% CI: 1.3, 3.1). (Murr, 2007). Similarly, Nguyen and colleagues report a similar relationship between mortality and hospital volume: compared to centers that performed less than 50 procedures a year, the odds of mortality were one third less among centers that performed 100-199 procedures (OR 0.65; 95% CI: 0.21, 0.45) (Nguyen, 2013).

Key Question #3: What are the potential short- and long-term harms of bariatric surgery procedures, including rates of procedure-specific and general surgical complications, longer-term morbidity, mortality, and requirements for procedure revision and/or reversal?

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 Table ES-4 on the following page. 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. 6.2), 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 has the highest complication rate (31.6%). Most studies were small and underpowered to detect any statistical differences between procedures for adverse events, 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 cohorts 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 ES-4 on the following page 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 data for each study can be found in Appendix D; in addition, findings are reported in detail for each surgical comparison in the sections that follow. A summary discussion of findings from retrospective cohort studies and case series is available in the full report.

Table ES-4: 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.

BPD = Biliopancreatic Diversion, LAGB = Laparoscopic Adjustable Gastric Banding, RYGB = Roux-en-Y Gastric Bypass, VSG = Vertical Sleeve Gastrectomy

Randomized Controlled Trials

Gastric Bypass vs. Sleeve Gastrectomy

We found only one good quality RCT (Schauer, 2012) that compared RYGB to VSG and included data on harms. This study evaluated 150 patients (mean age 49, 66% female, mean BMI 37) assigned to RYGB, VSG, or conventional weight-loss treatment and found that VSG had fewer reoperations (1 vs. 3) and fewer adverse events requiring hospitalization (4 vs. 11) than RYGB, but the study was underpowered to detect statistical differences between groups. No patients died, and there were no life-threatening complications for any study participant. During the three-year follow to this study (Schauer, 2014), with 91% patients remaining, additional minor complications occurred in both groups, (5 vs. 3 for RYGB and VSG, respectively) but there were no major late complications, reoperations, or deaths.

Three fair quality RCTs (Paluszkiewics, 2012; Kehagias, 2011; Peterli, 2013) also compared RYGB to VSG up to 3 years of follow-up, and all concluded that the procedures had similar outcomes with regards to safety. The first study (Paluszkiewics, 2012) evaluated 72 patients (mean age 44, 86% female, mean BMI 47.4) over one year and found no significant differences for early (6 vs. 7 for VSG) or late (22 in each group) complications, or reoperations (1 vs. 0 for VSG). Another RCT (Peterli, 2013), which followed 217 patients (mean age 43, 72% female, mean BMI 43.9) for a mean of two years, found that while more patients in the RYGB group required reoperation (5 vs. 1 for VSG) and greater frequency of perioperative morbidity (19 vs. 9 for VSG), these differences were not statistically significant. The final RCT (Kehagias, 2011) included 60 patients (mean age 35, 60% female, mean BMI 45.4) with the longest duration of follow-up (3 years) found that early morbidity was more common in the VSG group (13 vs. 10 for RYGB), though this difference was not statistically significant. In addition, while significantly more patients experienced vitamin B12 deficiency after RYGB (7 vs. 1 patient for VSG, p<0.05), reoperations and late morbidity occurred with the same frequency in both groups. There was one death related to surgery among all 176 patients in the RYGB group, which was result of gastrojejunostomy leakage.

Gastric Bypass vs. Gastric Banding

There were two good-quality RCTs (Angrisiani, 2007 and Angrisiani, 2013; Courcoulas 2014) comparing RYGB to LAGB. One of these studies (Angrisani, 2007) evaluated 51 patients (mean age 34, 82% female) mean BMI 43.6) undergoing LAGB or RYGB over a five-year period. During the perioperative period, two

patients in the RYGB group had reoperations – one patient had a conversion to laparotomy and another had a jejunal perforation requiring surgical intervention. No patients in the LAGB cohort had any complication requiring an additional procedure, but it is not clear if other minor complications occurred. After 30 days, two LAGB patients required a reversal surgery and one RYGB patient had a small bowel obstruction requiring another surgery. In the 10-year follow-up to this RCT (Angrisani, 2013), an additional seven operation occurred in the LAGB group, all of which were the result of band removal, while three occurred in the RYGB group, bringing the total number of overall complications to nine in the LAGB group and eight in the RYGB group. Study retention was more than 80% for both cohorts, and no patient died. Another RCT (Courcoulas, 2014) of good quality followed 69 patients (mean age 47, 81% female, mean BMI 35.5) for one year and found that more LAGB patients experienced an adverse event (3 vs. 1 for RYGB), including one reoperation to replace a detached port. No patient died in any study.

Conversely, a fair quality RCT (Nguyen, 2009) of 197 patients (mean age of 44, 77% female, mean BMI 47) found that subjects in the RYGB cohort experienced significantly more complications than those undergoing LAGB (50 vs. 15 patients, p<0.01). Nearly half of the complications in the RYGB cohort occurred in the perioperative period, seven of which were major complications including postoperative bowel obstruction in five patients and postoperative gastrointestinal hemorrhage in two patients. Only two major complications, including one gastrointestinal hemorrhage and an internal herniation, occurred in the LAGB group during the same time period. Although late complications were also more frequent in the RYGB group (43 vs. 10 for LAGB), fewer patients had a reoperation, though this difference was not statistically significant (8 vs. 10 for LAGB). The mean follow-up for the LAGB cohort was shorter (3.6 vs. 4.2 years) and had fewer subjects available for assessment (80 vs. 92 patients) than the RYBG group, so late complications and reoperations may be underreported. There were no deaths over the entire study period.

Gastric Bypass vs. Biliopancreatic Diversion (With or Without Duodenal Switch)
We identified five reports of three RCTs (Hedberg, 2012; Mingrone, 2012; Risstad, 2015; Søvik, 2010 and Søvik, 2011) comparing the differences between RYGB and BPD, all of which were of good quality. However, no study had more than 60 patients and only one RCT (Søvik, 2010; Søvik, 2011; Risstad, 2015) was powered to detect statistical differences. In this study, which evaluated 60 patients (mean age 36, 70% female, mean BMI 55) over one year, no differences were found for early (4 vs. 7 for BPD) or late complications (5 vs. 9 for BPD), or reoperations (2 vs. 1 for BPD), though the RYBG had fewer occurrences throughout the study period. After an additional year of follow-up (Søvik, 2011), there were an additional 10 complications and six reoperations for RYGB, and an additional six complications and one reoperation in the BPD group. For the RYGB patients, most of these late complications included cholelithiasis and abdominal pain, while patients in the BPD group experienced more frequent occurrences of vomiting and malnutrition. After five years of follow-up, the overall complication rate was comparable between groups, but BPD/DS was associated with a significantly higher rate of hospital admission (59% vs. 29%, p=0.02) and complications requiring surgical intervention (45% vs. 10%, p=0.002) (Risstad, 2015).

In the Hedberg study (Hedberg, 2012), which followed 47 patients (mean age of 48, 47% female, mean BMI 36.6) for a mean of 4.2 years, overall complications were relatively infrequent for both groups, with a total of five reoperations (2 vs. 3 for BPD) and seven readmissions (3 vs. 4 for BPD), though occurrences were again less common for RYGB patients. The final RCT (Mingrone, 2012) evaluated 60 patients (mean age 43, 53% female, mean BMI 45.2) over two years and found that the number of

reoperations was similar (1 in each group), but more overall complications occurred in patients undergoing BPD (6 vs. 3) compared to RYGB. One patient in each group died across all three studies.

Prospective Cohort Studies

All prospective comparative cohorts with harms data were of fair or poor quality, with the exception of one (Bowne, 2006). This study evaluated 106 super morbidly obese patients (mean age 42.5, 80% female, mean BMI 56) allocated to receive either RYGB or LAGB and followed for a median of 16.2 months. Although RYGB was associated with more early complications (11 vs. 3 for LAGB), the difference was not statistically significant. However, after the first 30 days through the end of the study period, there was a significantly greater incidence of late complications in the LAGB group relative to RYGB (43 vs. 11, p<0.05), including significantly more reoperations (15 vs. 3, p=0.04). One patient died in the LAGB cohort following elective band removal.

One prospective study (Hutter, 2011) of fair quality compared three of the four procedures of interest (RYGB, VSG, and LAGB), and had a larger sample size than all the other fair quality prospective studies combined. A total of 28,616 patients (mean age 45.2, 77% female, mean BMI 46.2) were evaluated over a period of one year; the study only reported on complications within the 30-day perioperative period, however. Thirty-day morbidity was highest in the open RYGB group (14.98%), followed by laparoscopic RYGB (5.91%), VSG (5.61%), and LAGB (1.44%). Thirty-day reoperation rates followed the same pattern (5.06%, 5.02%, 2.97%, and 0.92% for open RYGB, laparoscopic RYGB, VSG, and LAGB, respectively, as did 30-day rate of hospital readmission (9.41%, 6.47%, 5.40%, and 1.71%). Overall, both laparoscopic RYGB and VSG had significantly higher risk-adjusted morbidity, readmission, and reoperation rates compared to LAGB, but VSG had a significantly lower risk-adjusted reoperation rate compared to laparoscopic RYGB. Perioperative mortality ranged from 0.08% to 1.1% across groups, but rates did not differ statistically between them.

Harms of Bariatric Surgery in 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 adverse events, of which eight were hospital admissions due to depression or hypertension. Twelve patients experienced 13 adverse events 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 8 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. There was only one death due to cardiac failure during the study period which occurred in the RYGB group.

Key Question #4: What is the differential effectiveness and safety of bariatric surgery procedures according to health-system and/or program factors such as:
   a.   Surgeon experience
   b.   Procedure volume
   c.   Certification of surgery center
   d.   Members of core team
   e.   Type of pre-procedure preparation/post-procedure support

Surgeon experience has been primarily assessed through 'learning curve' studies in which patients are stratified into consecutive groups in order to compare outcomes between the first cohort receiving a particular procedure with later groups. Most learning curve studies have reported outcomes for RYGB patients; we found no studies related to BPD/DS. Operative times, complication rates, and length of hospital stay appear to decrease over time for RYGB, LAGB, and VSG, but results vary by surgeon and institution. Many studies report an inverse relationship between hospital/surgeon volume and adverse events, but concerns that sampling effects in low-volume settings may inflate estimates of harm have been voiced. Evidence is inconsistent as to whether accredited centers improve outcomes after bariatric surgery. It has been difficult to determine whether differential outcomes result from the volume requirements of certification, other standards of certification, or if effects are falsely inflated by smaller samples in non-accredited low volume facilities. There are very few studies that address members of the core team in relation to bariatric surgery outcomes. Two studies found that multidisciplinary teams reduce complications and improve chances for successful weight loss. Finally, the majority of studies related to pre-operative weight loss and support groups report that these interventions do not improve post-operative weight loss or resolution of comorbidities. Post-operative support groups, however, have been shown to help patients make positive lifestyle changes, improve psychological comorbidities, and achieve greater weight loss.

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 stratify patients into consecutive groups and compare 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 biliopancreatic diversion 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.

RYGB

Although it is a technically demanding procedure, implementation of RYGB as part of a surgical training fellowship has been shown to be safe under the supervision of an experienced surgeon. Among bypass patients, fellowship training programs have been credited with shortening operative times and improving perioperative outcomes during a surgeon's early experience with the procedure (Gonzalez,

2007; Iordens, 2012; Oliak, 2004). Gonzalez, Nelson, and Murr (2007) and Oliak, Owens, and Schmidt (2004) found that fellowship training programs reduced operative times by 33-35%.

During the initial learning phase, operative times vary tremendously according to individual facilities and surgeons. Despite individual and institutional variation, learning curve studies almost invariably report significant decreases in operative time, length of hospital stay, and complications between early and later consecutive cases (Pournaras, 2010; Chen, 2012; Ballesta-Lopez, 2005; Huang, 2008; Shikora, 2005; Søvik, 2009; Andrew, 2006; Schaeffer, 2008; Schauer, 2003; Papasavas, 2002). In one of the larger learning curve studies of 750 patients, Shikora and colleagues found that the mean operating time decreased from 212 to 132 to 105 minutes in cases 1-100, 101-200, and 201-300, respectively (Shikora, 2005).

VSG
We found four studies that measured patient outcomes in relation to surgeon experience with laparoscopic VSG (Daskalakis, 2011; Prevot, 2014; Zachariah, 2013; Zacharoulis, 2012). Daskalakis et al. (2011) compared the outcomes of VSG patients who were operated on by surgeons with varying levels of experience. The researchers found that rates of overall and major complications did not differ among individual surgeons or between the early and late period of experience for the three surgeons. However they did notice that the mean operating time decreased from 68 minutes to 54 minutes after the first 115 cases (p<0.001).

The remaining sleeve gastrectomy learning curve studies followed the first consecutive patients (sample size ranged from 84 to 228 cases) to undergo sleeve gastrectomy at the authors' respective institutions and stratified patients into two or three groups of 28-50 according to case sequence (Prevot 2014; Zachariah 2013; Zacharoulis 2012). Prevot et al. (2014) not only found a significant reduction in operative time after the first 28 cases (138.8 minutes vs. 93 minutes in the following 28 cases, p<0.01), but also a greater percentage of excess weight loss after 5 years (33.6% vs. 47.9%, p=0.042). In a study of the first 102 VSG cases at their institution, Zacharoulis et al. found significant reductions in operative time and length of hospital stay after a threshold of 68 cases (Zacharoulis, 2012). While Zachariah and colleagues did not find a reduction in operative time or hospital stay over time, they did find that the overall complication rate declined from 8% to 1.68% (p=0.022) after the first 50 patients (Zachariah, 2013).

LAGB
We identified two studies that compared outcomes among LAGB patients across consecutive series (Shapiro, 2004; Breznikar, 2009). Similar to the findings for other procedures, researchers found that operative time and the overall number of complications reduced as surgeons' experience grew over time. For example, Shapiro and colleagues found that mean operating time reduced from 79 minutes to 59 minutes after the first 30 cases (p=0.004) and the complication rate fell from 37% to 7% (p=0.005) (Shapiro, 2004).

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 only focused 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 adverse events. Nguyen et al. (2004) found that in-hospital mortality was lower in academic medical centers with more than 100 RYGB cases/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 a RYGB operation was significantly higher at low volume hospitals ($13,908 $\pm$ $9573 versus $10,292 $\pm$ $6680 for high-volume, p<0.01).

Findings were similar in other large studies. Birkmeyer and colleagues (2010) found serious complication rates among Michigan patients of 4.1% (95% CI 3.0%, 5.1%), 2.7% (95% CI 2.2%, 3.2%), and 2.3% (95% CI, 2.0%, 2.6%) in low (<150 cases/year), medium (150-299 cases/year), and high volume hospitals ($\geq$300 cases/year), respectively (p<0.001). Based on data from the U.S. Nationwide Inpatient Sample for open and laparoscopic bariatric procedures, Gould et al. (2011) found that each incremental increase in volume of 25 cases yielded lower complication and mortality rates without an obvious threshold for best performance (Gould, 2007).

Murr et al. (2007), used the Florida-wide hospital discharge database to analyze the mortality and hospital volume relationship among gastric bypass patients, and found that mortality was lowest (0.1%) in the hospitals where 100-199 procedures were undertaken over a 5-year period compared to low volume (<10 procedures) hospitals (2.9%) and high volume hospitals (0.3%) in which more than 500 bypass procedures were performed. Hospitals in the 100-199 range also had the lowest complication rate (5%). The authors conclude that a threshold of 100-199 procedures over a five-year period might be an appropriate performance threshold.

The relationship between low volume facilities and poorer outcomes seems to hold true when considering hospital volume and surgeon volume together. Torrente and colleagues (2013) used gastric bypass data from the Pennsylvania Health Care Cost Containment Council to assess both surgeon and hospital volume. They found that low-volume surgeons (<50 cases per year) at low-volume hospitals (< 125 cases per year) had poorer outcomes, with 0.57% of patients dying in the hospital compared to high-volume surgeons (>50 cases per year) at high-volume hospitals (300 or more cases per year) (in-hospital mortality: 0.12%). Data from the Michigan Bariatric Surgery Collaborative registry reveal a similar trend in serious complication rates, which were about twice as high for low-volume surgeons (<100 cases per year) at low-volume hospitals (<150 cases per year) than for high volume surgeons ($\geq$250 cases per year) at high-volume hospitals ($\geq$300 cases/year) (Birkmeyer, 2010).   Finally, Weller and colleagues used discharge data in New York to assess differences in readmission rates, and found patterns similar to those described above (Weller, 2007).

Smith et al. (2013) note that technical factors may partially explain why high-volume surgeons (>100 RYGBs/year) have better results. Analyzing data from the Longitudinal Assessment of Bariatric Surgery (LABS), which included 3,412 RYGB procedures performed by 33 surgeons, Smith and colleagues calculated the relative risk of a composite endpoint, which was comprised of death, venous thrombosis, pulmonary embolism, reoperation, and nondischarge at 30 days, in relation to a number of intraoperative factors. The authors' findings indicate that high-volume surgeons are more likely to perform a linear stapled gastrojejunostomy (58% vs. 16%), use fibrin sealant (61% vs. 30%), and place a drain at the gastrojejunostomy (24% vs. 13%) during RYGB compared with low- volume surgeons (<25

RYGBs/year, p<0.0001 for all comparisons listed). However, after adjusting for these technical factors, the strength of the volume-outcome relationship was reduced from a relative risk of 0.93 to 0.90 per 10 RYGB/year. This suggests that technique alone cannot account for the volume-outcome relationship.

Certification

On February 21, 2006, the Centers for Medicare and Medicaid Services (CMS) released the National Coverage Determination (NCD) for Bariatric Surgery for Treatment of Morbid Obesity. This measure restricted coverage of bariatric surgery to procedures performed at facilities that were accredited by either the American College of Surgeons (ACS) as a "Level 1 Bariatric Surgery Center" or the American Society for Metabolic and Bariatric Surgery (ASMBS) as a "Bariatric Surgery Center of Excellence (COE)."

The effects of the NCD on health outcomes have proven challenging to measure, with many studies showing no or marginal differences. In a retrospective longitudinal study of 2004-2009 hospital discharge data from 12 states, Dimick et al. (2013) compared bariatric surgery outcomes before and after the NCD's publication in both Medicare and non-Medicare patients (n=321,464). While complication and reoperation rates improved during the study period in both groups, this trend was already occurring prior to the coverage decision. After controlling for time trends, patient factors, and changes in procedure type (to account for a shift away from open RYGB to laparoscopic RYGB and LAGB), there were no statistically-significant changes in outcomes after the NCD. For example, the complication rate was 8.0% after the NCD vs. 7.0% before (relative risk 1.14, 95% CI: 0.95, 1.33) (Dimick, 2013).

Evidence suggests that the impact of the NCD may have been more social than clinical, including unintended consequences for minority populations (Nicholas and Dimick, 2013). Nguyen et al. (2010) observed an initial 29.3% reduction in the number of procedures performed among Medicare patients, although these numbers eventually surpassed baseline levels within two years after the NCD's publication. Restricting care to accredited facilities was also associated with a relative decline in the proportion of nonwhite Medicare patients receiving bariatric surgery (Nicholas and Dimick 2013). Furthermore, Livingston et al (2010) observed that the median distance Medicare patients were required to travel to receive care at a COE increased from 25 miles to 46 miles after publication of the NCD.

Other studies have sought to determine whether accreditation improves clinical outcomes. Livingston (2009) used the 2005 National Inpatient Survey from the Healthcare Cost and Utilization Projects (HCUP-3) to compare outcomes at COE-designated and non-designated programs. The author reported that both the hospital mortality rate and complication rate did not statistically differ between COEs and non-COEs (Livingston, 2009). Similarly, Birkmeyer et al (2010) did not find significant differences between adjusted rates of serious complications between COE hospitals and non-COE hospitals.

In contrast to the findings stated above, Nguyen and colleagues evaluated outcomes for bariatric procedures performed at academic centers with COE status vs. non-accredited academic centers in nearly 36,000 patients (Nguyen, 2012). In-hospital mortality (0.06% vs. 0.21%, p=0.003) and hospital length of stay (2.4 vs. 2.7 days, p<0.001) differed significantly in favor of accredited centers, and overall hospital costs were also lower. However, the authors noted that they were unable to determine conclusively whether the findings observed in the study were due solely to accreditation, procedure volume, or a combination of both.

In an attempt to account for these uncertainties, Jafari and colleagues (2013) used the HCUP-3 Nationwide Inpatient Sample to analyze risk-adjusted outcomes for RYGB and VSG cases in accredited (n=216,000) versus non-accredited (n=20,219) high-volume centers ($\geq$ 50 cases annually). The authors found that non-accredited centers were associated with higher rates of in-hospital mortality (OR 3.57; 95% CI: 1.49, 8.33) but lower rates of serious morbidity (OR 0.84; 95% CI: 0.71, 0.98) (Jafari, 2013). The in-hospital mortality rate of high-volume non-accredited centers was comparable to that of low-volume centers (0.22 vs. 0.17%, respectively), suggesting that the standards associated with accreditation were more important predictors of outcome than annual case volume.

In April 2012, the ASMBS and the ACS formed the Metabolic Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP). This unified national accreditation program maintained many of the standards of the previous programs, but adjusted volume requirements to 50 or more cases per year. Despite this change, CMS removed the requirement that bariatric surgical procedures be performed at an accredited facility in September 2013, citing evidence that outcomes were comparable at accredited and non-accredited facilities (CMS, 2013).

Members of Core Team

Very few studies have examined the differential effectiveness of multidisciplinary care across the various bariatric procedures. This is most likely because multidisciplinary care is required for accreditation as a COE; the team generally includes nutritionists, psychologists, pulmonologists, cardiologists and other medical specialists trained in bariatric care. In a nationwide 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 analyzed 2-year predictors of success, which they defined as EWL>50% (Chevallier, 2007). The authors found that patients who did not change their eating habits after surgery were 2.2 times less likely to have weight loss success (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). Although they did not directly measure the effects of a multidisciplinary team, the authors emphasized that these findings were indicative of the need to employ a multidisciplinary team before and after the operation (Chevallier, 2007).

Furthermore, a team approach, as compared to a single surgeon approach, may reduce operative times and shorten hospital stays among patients undergoing laparoscopic RYGB (Chen 2012). We found a single study that compared outcomes between 200 RYGB patients who either received care through a multidisciplinary team approach or from an individual surgeon (mean age 31, 62% female, mean BMI 43 kg/m^2) (Chen, 2012). Twelve months post-surgery, patients treated by the multidisciplinary team lost a greater percentage of overall weight than those treated by an individual surgeon (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 group. As mentioned in Key Question 2, the authors credited these improved outcomes to regularly scheduled appointments with a specialized dietician as well as to surgeons being given more time to focus on improving their technique.

Type of Pre-procedure Preparation/Post-procedure Support

Pre-operative interventions such as dietary counseling or weight loss programs are mandated by a growing number of insurance payers despite a lack of evidence that these measures improve outcomes. An RCT of 55 patients (mean age 46, 83.5% female, mean BMI 45.5 kg/m^2) who were randomized to participate in a medically supervised weight management program in the six months prior to LAGB surgery did not produce significant differences in post-operative weight loss from those who received usual pre-operative care (Parikh, 2012).

In another RCT, 100 patients (mean age 44, 84% female, mean BMI 49 kg/m^2) were randomized to either lose 10% of their body weight or not prior to gastric bypass (Alami, 2007). Although the researchers reported greater short term (3 month) EWL in the weight loss group (44.1% vs. 33.1%; p=0.0267), these differences were no longer significant by 6 months of follow-up (53.9% versus 50.9%; p=NS). Moreover, major complications, intraoperative complications, conversion, and resolution of comorbidities were not significantly different between groups, although the weight loss group had on average a 37.4-minute shorter operative time.

A third RCT, which randomized 298 patients (mean age 40, 70% female, mean BMI 43 kg/m^2) to receive a two-week very low calorie diet (VLCD) or no diet prior to RYGB, had slightly different results (Van Nieuwenhove, 2011). Although operative times and intraoperative complications did not differ between groups, the authors did observe significant differences in 30-day morbidity (8 in VLCD vs. 18 in controls, p=0.04).

Despite the possibility that pre-operative weight loss reduces 30-day morbidity, the majority of available cohort studies indicate that these programs do not correlate with post-operative weight loss. In a retrospective analysis of 539 patients receiving gastric bypass, banding, or sleeve gastrectomy, Becouarn, Topart, and Ritz (2010) did not find a relationship between pre- and post-operative weight loss, regardless of the surgical technique performed. They suggest that while pre-operative weight loss can reduce the difficulties of surgery, the advantages for long-term weight loss are not validated. Correspondingly, three retrospective analyses of RYGB patients who participated in pre-operative weight loss programs found that these programs were not associated with better excess weight loss 1-2 years after the surgery (Carlin, 2008; Harnisch, 2008, Huerta, 2008) or in terms of resolution of comorbidities (Harnisch, 2008). Finally, another cohort study documented potentially negative consequences of mandated pre-operative weight loss: Jamal and colleagues (2006) found that the pre-surgery dropout rate among 322 RYGB patients was 50% greater in a group whose insurance mandated that patients participate in 13 weeks of pre-operative dietary counselling compared to patients without such a requirement (p<0.05).

A single study of 548 patients, which retrospectively stratified results by percentage of pre-operative weight loss, found that patients who lost more than 10% of their weight prior to surgery had greater excess weight loss 12 months after RYGB than patients who lost less than 5% (72.7% vs. 63.1%, p=0.015) (Giordano, 2014). However, the authors of this study identified several limitations that may have biased the results, including imbalance in demographic and clinical characteristics between weight-loss groups, variable pre-operative weight loss methods, lack of control for site/surgeon effects, and attrition of the sample (loss to follow-up was identified as a limitation but the rate was not reported).

Patient adherence to pre- and post-operative procedures 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). Gould and colleagues had similar findings after following gastric bypass patients 3-4 years post-operatively. The authors found that patients who attend all scheduled post-operative appointments achieve better 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) (Gould, 2007).

Although pre-procedure support groups have had little success in improving post-operative lifestyle changes (Lier 2012), there is some evidence that post-operative support groups help patients to make

positive lifestyle changes, improve psychological comorbidities, and have 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 excess weight loss (80% versus 64%; p<0.001) and BMI reduction (6.48 vs. 3.63, p<0.001) (Nijamkin 2012).

Key Question #5: What is the differential effectiveness and safety of bariatric surgery procedures according to patient and/or clinical factors such as:

  a. Age
  b. Gender
  c. Race/ethnicity
  d. BMI
  e. Presence of comorbidities
  f. Prior event history
  g. Smoking status
  h. Psychosocial health
  i. Pre/post procedure adherence with program recommendations

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/clinical factors is largely inconclusive. There is some evidence that patients in older age categories experience fewer complications when undergoing LAGB compared to VSG or RYGB. Evidence of different weight and complication outcomes is inconsistent when stratified by gender. Although males tend to have higher rates of overall complications, one study found a higher prevalence of long term complications among female LAGB patients compared to male LAGB patients. A statistical difference in long term complications was not found for RYGB males and female. Outcomes are rarely stratified by race/ethnicity, and comparisons are confounded by different body composition in some racial categories (e.g., Asian vs. European/Caucasian). Patients in higher BMI categories are more likely to experience longer operative times and hospital stays; while these patients tend to lose a higher percentage of pre-operative BMI than those in lower BMI categories, the percentage of excess weight loss appears to decline as BMI increases. Rates of complications and post-surgical hypothyroidism are greater for hypertensive patients undergoing RYGB than LAGB. Other comorbidity data are inconclusive. Adherence to pre- and post-operative programs may improve post-surgery weight loss for LAGB patients, but appears to have a neutral impact on RYGB patients. We found no studies that stratified outcomes by prior event history, smoking status, or psychosocial health that met our inclusion criteria.

There is a paucity of RCTs and prospective comparative cohort studies comparing the differential effectiveness of specific bariatric procedures on various patient subgroups. Available studies have been relatively inconsistent in reporting, defining, and measuring outcomes for key subgroups. As such, evidence about the differential effectiveness and safety of bariatric surgery procedures according to patient/clinical factors is largely inconclusive. Given the scarcity of such data, we have included

retrospective and lower-quality studies in the sections that follow. Results should be interpreted with caution.

Age

Older patients are more susceptible to complications and may not lose as much excess body weight as their younger counterparts. In a matched cohort study of 8,847 patients (mean age 46, 74% female, mean BMI 48), Carlin et al. (2013) examined 30-day serious complications by age category and found that, across all procedures, serious complications increased in patients over 50 years of age relative to patients in younger age categories.   When individual procedures were compared, rates of serious complications did not statistically differ between RYGB and VSG. However, when VSG and LAGB were compared, rates were significantly higher among VSG patients starting at age 40 and above.

Pohle-Krauze and colleagues found a differential effect on LDL cholesterol by age group in a retrospective comparison of 294 RYGB and LAGB patients (mean age 45.6, 84% female, mean BMI 47) (Pohle-Krauza, 2011).   Between baseline and 42 months postoperatively, LDL cholesterol significantly decreased in RYGB patients aged 47 and above, while LAGB patients of the same age experienced a non-significant _increase_ in LDL levels. Differences in LDL cholesterol values were not statistically-significant in patients younger than 47 for either procedure.

Gender

Studies that stratified outcomes by both gender and procedure type did not report consistent weight-loss patterns. For example, Nguyen et al. (2013), found no differences in weight loss between genders during the first three years after RYGB or LAGB but did note that LAGB males had a greater reduction in BMI than females receiving the same procedure beyond three years (-8.2 versus -3.9 kg/m2, p= 0.02). Among adolescents receiving these same procedures, Messiah et al. (2013) found that RYGB resulted in a BMI percentile decrease approximately twice that of LAGB among boys (-3 vs. -1.5 percentile points) but more than _four_ times that of LAGB among girls (-9 vs. -2) after one year of follow-up. Breznikar et al. (2009) reported EWL after one year of follow-up and noted that female adults had a greater mean EWL than males after LAGB (54% versus. 40.9% respectively) but not after VSG (52.1% versus 65.7%), although the significance of these differences was not reported. Similarly, Bekheit (2014) found a significant difference in EWL between 35 male and 254 female LAGB patients (males: -0.59% vs. females: 36.9%, p=0.002) but similar rates of EWL by gender among those undergoing RYGB.

As discussed in Key Question 2, males tend to have higher complication rates than females. However when outcomes are stratified by both gender and procedure type, the evidence is rather inconsistent. For example, in a retrospective study that compared 1,295 RYGB and LAGB patients (mean age 40, 81% female, mean BMI 43.6) Nguyen NQ et al. (2013) reported similar rates of longer-term complications in male and female RYGB patients but not in male and female LAGB patients: longer-term complications were shown to be far less likely in male LAGB patients than female LAGB patients (male: 2/131 [1.5%] versus female: 59/555 [10.6%], p <0.001).

Race/Ethnicity

We found a single study that stratified outcomes by race/ethnicity. Although it was not included in our formal review, we include it here as the only study that stratified outcomes by both race and procedure type. In an analysis of New York's inpatient hospital discharge database, Lindsey et al. (2009) identified 8,413 adults who underwent RYGB or LAGB during calendar year 2006. The authors found statistically significant differences in complication rates across race/ethnicity categories for LAGB patients (2.6% for

white or black non-Hispanic, 3.9% for Hispanic, and 6.3% for other/unknown [Asian, Native American, Hawaiian/Pacific Islander], p<0.001) but no differences among those undergoing RYGB.

Four studies were conducted exclusively on Asian populations (Lee, 2010; Liang, 2013; Wong, 2009; Yong, 2012). Previous studies have ascertained that certain Asian populations have a higher percentage of body fat than white or European populations as well as a higher prevalence of both type 2 diabetes and cardiovascular risk factors in levels of BMI lower than those classified by the World Health Organization (WHO) as overweight or obese (WHO, 2004). Because of the disparities between Asian and European body composition, some Asian investigators performed surgery on patients at lower levels of BMI than is typical of U.S. or European studies (i.e., ≥40 or ≥35 with comorbidities). The four studies meeting our inclusion criteria from Asian populations had baseline BMIs between 30 and 42 and were followed for 6-36 months. The RYGB patients in Lee's study experienced greater excess weight loss compared to five other studies of RYGB patients from Europe or the United States (83% vs. 52-75%) that had similar durations of follow-up and baseline BMI (Cutolo, 2012; Leslie, 2012; Puzziferri, 2008; Vidal, 2013; Weber, 2004). However when compared to LAGB patients from U.S. or European studies, the patients in Lee et al.'s study experienced less excess weight loss (30% vs. 42-79%) (Dixon, 2012; O'Brien, 2010; Puzziferri, 2008; Sabbagh, 2010; Weber, 2004). Because the other Asian studies included in our review either did not report EWL, did not report baseline BMI, or did not have comparative lengths of follow-up with any non-Asian studies, it is impossible to comment whether Lee et al.'s findings are consistent across other Asian patients.

BMI

Patients with higher preoperative BMIs experience lower levels of excess weight loss than patients with lower preoperative BMIs. For example, in a retrospective comparative cohort study of 1,261 patients, Biertho and colleagues found that after 18 months follow-up, EWL for patients with a BMI between 50 and 60 was 69% and 33% among RYGB and LAGB patients, respectively (Biertho, 2003). Patients with lower preoperative BMIs (between 40 and 50) experienced greater EWL for both procedures, but the difference between them also widened somewhat (81% and 40%, respectively).

Similarly, Puzziferri et al.'s (2008) prospective cohort study reported that over two years, mean excess weight loss was greater for those who had a preoperative BMI≤50. RYGB patients who had a preoperative BMI >50 had 0.12 times the odds of successful weight loss (EWL≥40%) after 6 months postoperatively than those with a preoperative BMI of 50 or below (95% CI: 0.08, 0.18). LAGB patients with a preoperative BMI greater than 50 followed the same pattern, with a 0.13 odds ratio of successful weight loss (95% CI: 0.06, 0.29). Although this effect diminished over time among RYGB patients and was no longer statistically significant after 18 months of follow-up, LAGB patients with a higher pre-surgical BMI remained significantly less likely to have successful weight loss (OR 0.43; 95% CI: 0.24,0.78). One study stratified procedure-related parameters by BMI category and procedure type (Stephens, 2008). The authors found that length of hospital stay was significantly longer for RYGB patients with a baseline BMI ≥60 relative to RYGB patients with a starting BMI <60 (3 vs. 2 days hospital stay, p<0.05), but that operative time did not significantly differ. These measures did not statistically differ by BMI category among LAGB patients.

The RCTs and comparative cohorts evaluated in this assessment are summarized in **Table ES-5** beginning on page ES-42 according to the mean baseline BMI reported in each study and the median values of six outcomes related to surgical success (% change in BMI, %EWL, and improvement/resolution of type 2 diabetes, hypertension, dyslipidemia, and sleep apnea). While the evidence presented in this table

indicate certain trends, it should be interpreted with caution as the reported medians are composites of good, fair, and poor quality studies. Also, given that studies did not use a uniform definition for improvement or resolution of comorbidities, the results should be interpreted with caution.

Table ES-5 indicates that higher BMI groups, particularly those with a BMI>50, experience a _greater_ percent change in BMI than patients with an initial BMI of 30-34.99 after RYGB (34% vs. 25%), VSG (36% vs. 21%), and BPD/DS (43% vs. 32%), but _not_ LAGB (18% vs. 17%). Interestingly, the opposite trend is apparent when EWL is used as the measure of surgical success: with the exception of BPD/DS, patients in higher BMI categories appear to experience _less_ excess weight loss than patients with lower BMIs. As noted previously, most of the studies in our sample that evaluated comorbidity resolution as an outcome were focused on patients with BMI levels >40; as such, data are limited for comparisons across procedures and BMI categories. The most frequent comorbidity evaluated was type 2 diabetes; rates of resolution tended to increase with greater levels of BMI for RYGB (from a median of 64.7% for BMI 30-34.9 to 77.1% for BMI >50), VSG (from 50.0% to 88.9%), and BPD/DS (from 84.8% to 91.4%), with no discernible trend apparent for LAGB.

Comparative Studies in Patients with BMI <35
A growing number of comparative studies have focused on patients with more moderate levels of obesity (i.e., BMI <35), with accordingly increased interest in this population among clinicians and payers. Among our set of good- and fair-quality RCTs and prospective cohort studies, a total of nine enrolled patients with BMIs at this level (Courcolas, 2014; Dixon, 2007; Dixon, 2008; Halperin, 2014; Ikramuddin, 2013; Kashyap, 2013; O'Brien, 2006; Schauer, 2012; Scopinaro, 2011). A tenth RCT (Liang, 2013) is not included in this discussion because it was performed in China; differences in body composition and fat distribution between Asian and Western populations are discussed on the previous page.

Importantly, seven of the ten studies included presence of type 2 diabetes 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 those studies in this set with a mean preoperative BMI of 30-34.9 are summarized in **Table ES-5** on pages ES-42 through ES-43; patterns of weight loss across procedures were similar to those in studies of patients at higher BMI.

More broadly, however, all of the seven studies involving lower BMI levels (including those with a mean preoperative BMI slightly above 35) that measured complete type 2 diabetes 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 diabetes (e.g., reduced HbA1c, reduced insulin use) showed between-group differences of even greater magnitude.

Table ES-5: Key clinical outcomes of RCTs and prospective cohort studies, stratified by mean pre-operative BMI

		Baseline Mean BMI Category							
		30-34.99		35-39.99		40-49.99		>50	
		Median	Range	Median	Range	Median	Range	Median	Range
% Decrease BMI	RYGB	25.4	(19.6-34.3)	26.0	(24.1-33.1)	32.2	(7.5-52.3)	34	(10.1-46.7)
	VSG	21.3	(21.3-21.3)	22.0	(19.1-22.5)	28.4	(15.0-37.1)	30.1	(11.0-39.4)
	LAGB	16.8	(11.8-21.7)	16.8	(13.0-17.5)	20.4	(6.0-46.8)	17.7	(1.0-31.8)
	BPD/DS	31.8	(17.3-46.3)			32.6	(15.9-50.8)	43.4	(39.2-47.7)
	Follow-up (months)	12.0	(3.0-45.2)	15.3	(12.0-60.0)	12.0	(0.5-120.0)	22.6	(1.2-84.0)
	No. Studies	7		6		79		22	
	Good/Fair/Poor	2/3/2		3/1/2		9/34/36		4/10/8	
% EWL	RYGB	70.0		77.0	(61.0-92.9)	67.0	(27.1-88.0)	61.8	(43.8-72.3)
	VSG			58.5	(51.0-66.0)	59.2	(30.7-83.0)	47.5	(25.4-75.0)
	LAGB	87.2		50.1	(34.0-62.5)	43.5	(18.2-78.8)	45.9	(31.0-73.0)
	BPD/DS					52.7	(34.9-70.4)	73.4	63.0-84.0)
	Follow-up (months)	18.0	(12.0-24.0)	30.0	(18.7-60.0)	24.0	(0.47-120)	24.0	(12.0-84.0)
	No. Studies	2		4		57		15	
	Good/Fair/Poor	1/0/1		1/1/2		6/27/24		1/8/6	
% Improvement Hypertension	RYGB			90.0		71.0	(22.0-100.0)	62.6	(60.7-69.2)
	VSG					64.3	(23.5-100.0)		
	LAGB			40.0		57.5	(18.0-100.0)	54.3	(33.3-66.7)
	BPD/DS	67.0				81.4	(68.6-87.0)	68.3	(66.7-69.9)
	Follow-up (months)	36.0		60.0		21.0	(3.5-84.0)	24.0	(12.0-50.4)
	No. Studies	1		1		29		5	
	Good/Fair/Poor	0/1/0		0/0/1		4/12/13		1/3/1	

Baseline Mean BMI Category								
		30-34.99		35-39.99		40-49.99		>50	
		Median	Range	Median	Range	Median	Range	Median	Range
% Improvement T2DM	RYGB	51.1	(33.0-92.3)	73.4	(66.7-80.0)	79.0	(33.0-100.0)	77.1	(40.0-100.0)
	VSG	50.0	(50.0-50.0)			77.3	(36.0-100.0)	88.9	(88.9-88.9)
	LAGB	33.0	(21.1-100.0)	50.0	(25.0-73.0)	50.0	(17.0-100.0)	52.3	(36.4-66.7)
	BPD/DS	84.8	(83.0-84.8)			87.1	(81.5-92.7)	91.4	(82.7-100.0)
	Follow-up (months)	12.0	(3.0-45.2)	24.0	(12.0-60.0)	16.0	(1.0-62.7)	24.0	(1.5-50.4)
	No. Studies	6		3		35		7	
	Good/Fair/Poor	0/3/3		2/0/1		3/14/18		1/4/2	
% Improvement Sleep Apnea	RYGB	89.0				70.5	(10.0-100.0)	56.7	(49.3-88.0)
	VSG					62.0	(6.0-99.0)		
	LAGB					29.0	(3.0-55.0)	46.2	(39.3-66.7)
	BPD/DS	90.0						79.5	(78.9-80.0)
	Follow-up (months)	45.15				21.6	(12.0-36.0)	20.1	(12.0-20.1)
	No. Studies	1		0		11		4	
	Good/Fair/Poor	0/0/1				2/5/4		1/3/0	
% Improvement Dyslipidemia	RYGB			100.0		64.5	(6.0-100.0)	52.9	(27.3-58.8)
	VSG					67.5	(35.0-67.5)		
	LAGB			38.0		36.5	(0.0-36.5)	34.4	(23.3-45.5)
	BPD/DS					90.0	(90.0-90.0)		
	Follow-up (months)			60.0		24.0	(12.0-62.7)	16.2	(12.0-50.4)
	No. Studies	0		1		18		3	
	Good/Fair/Poor	0		0/0/1		2/9/7		1/1/1	

BMI = Body Mass Index; BPD/DS = Biliopancreatic Diversion/Duodenal Switch; EWL = Excess Weight Loss; LAGB = Laparoscopic Adjustable Gastric Banding; RYGB = Roux-en-Y Gastric Bypass; T2DM = Type 2 Diabetes Mellitus; VSG = Vertical Sleeve Gastrectomy

An additional RCT evaluated the effects of LAGB vs. 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). 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, vs. 19% in the nonsurgical group (p<0.05).

Most of these studies also reported improvements in measures of cholesterol and hypertension, 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.

Comorbidities

Although many studies reported the prevalence of common obesity-related comorbidities among respective study populations, we found a single study that stratified outcomes according to both comorbidity and procedure type. Lindsey et al. (study characteristics described in race/ethnicity section) found that congestive heart failure and cardiac arrhythmia were associated with higher complication rates for the three procedure types: post-surgical complication rates were 40% for open RYGB, 21.1% for laparoscopic RYGB, and 17.4% for LAGB among patients with congestive heart failure (p<0.001), and 38.8%, 38.7, and 11.7% among those with cardiac arrhythmias (p<0.001); both sets of complication rates were significantly higher than for the overall cohorts (13.4%, 8.6%, and 3.1% for open RYGB, laparoscopic RYGB, and LAGB, respectively). Other comorbidities, including valvular disease, pulmonary circulation disorders, coagulopathy, and current drug abuse, were correlated with a greater risk of complications for open RYGB but not for laparoscopic RYGB or LAGB.

Rates of complications (3.8% vs. 2.3%, p=0.03) and postoperative hypothyroidism (0.9% vs. 3.3%, p=0.04) differed significantly for LAGB vs. RYGB among patients with hypertension at baseline, but did not differ among those without this comorbidity (Lindsey, 2009). Patients with peripheral vascular disorders who underwent RYGB had a significantly greater complication rate than those without this condition (32.0% versus 8.4%, p<0.001), but this difference was not observed among those undergoing LAGB (Lindsey, 2009).

Prior Event History
We found no studies that stratified outcomes by prior event history and met our inclusion criteria.

Smoking Status
We found no studies that stratified outcomes by smoking status and met our inclusion criteria.

Psychosocial Health
We found no studies that stratified outcomes by factors associated with psychosocial health and met our inclusion criteria.

Pre/post Procedure Adherence with Program Recommendations

We found a single retrospective comparative cohort study that stratified outcomes by adherence with pre-/post-operative program recommendations (mean age 43, 87% female, mean BMI 44) (El Chaar, 2011).   The study reported that LAGB patients who missed more than 25% of their pre-procedure appointments experienced 23% EWL at 12 months, compared with 32% for those who missed fewer appointments (p=0.01) (El Chaar, 2011).   However, no differences in RYGB performance were observed when stratified by pre-procedure appointment attendance.

Key Question #6: What are the costs and cost-effectiveness of the major bariatric surgery procedures of focus in this evidence review?

Published evidence accumulated to date 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. Findings from our own decision model confirm this, with results that are robust to even extreme assumptions about the durability of treatment effect and the impact of bariatric surgery on mortality. Our model does suggest, however, that bariatric surgery is most cost-effective in morbidly-obese individuals, and that cost-effectiveness erodes somewhat as BMI levels decrease.

Prior Published Evidence on Costs and Cost-Effectiveness

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 quality of life (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 open 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 quality-adjusted life year (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 U.S. populations are summarized in detail on the following page.

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. In 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 the shorter-term (5-year) cost impact of surgery vs. standard care, and 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 was $6,600, $17,200, and $6,200 per QALY, respectively, gained 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).

ICER Simulation Model: Methods

In order to augment the available evidence on the economic impact of bariatric surgery, and to compare all procedures of interest in this evaluation, we developed our own decision-analytic model. Where available, we included payment data from the HCA in our evaluation. The focus of attention in our model was on all four procedures of interest (i.e., RYGB, LAGB, VSG, and BPD/DS) in comparison to standard nonsurgical management for all obese individuals (BMI≥30) as well as in subgroups defined by BMI range (i.e., 30-34.9, 35-39.9, and ≥40). 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 surgery. This analysis compared change in BMI, and proportions of patients with perioperative mortality, reoperation, and medical complications, as well as the proportions of patients with remission of diabetes, hypertension, hyperlipidemia, and sleep apnea. Costs of interest included those of treatment, reoperation, management of complications, and total costs. A schematic of the model can be found in **Figure ES-9** on page ES-48.

In addition, to explore the potential impact of obesity and its treatment on quantity and quality of life, a cost-utility analysis was also conducted over a 10-year time horizon based on assumed trajectories

of BMI change after the various forms of surgery and standard care. All analyses were conducted using Microsoft Excel 2010 (Microsoft Corporation, Seattle, Washington).

Detailed information on model methods, sources for data on effectiveness, harms, costs, and quality of life, and other information can be found in the full report.

ICER Simulation Model: Results

Reference Case Analysis – Bariatric Surgery Versus Standard Care (One-year Time Frame)

A change in BMI is a measure of effectiveness for the model using a one-year time frame. This model also includes the complications which occur in year 1. When compared with standard care in all patients with obesity (BMI≥30), the use of RYGB, VSG, LAGB, and BPD/DS was associated with an approximate decrement in BMI of 10.4, 9.8, 7.8 and 12.5, respectively. RYGB, VSG, LAGB, and BPD/DS costs $30,099, $24,357, $22,035, and $42,979, respectively (see **Table ES-6** beginning on page ES-49). 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.

We also stratified results by BMI sub-categories. Overall, the findings for BMI are more favorable for patients within the morbidly obese category (BMI≥40) compared with those with lower BMI. For example, patients using RYGB and having BMI≥40 achieved larger absolute and percentage reductions in BMI (11.7, 29%) compared with those who had BMI 30-34.9 (8.45, 26%). The same trend occurred for other bariatric surgery procedures. 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. Similarly, resolution of comorbidities was more frequent among those with higher BMI categories. We attempted to gather data related to sleep apnea resolution but data were too limited, particularly when stratified by BMI.

Figure ES-9: Decision model for short and long-term economic outcomes of bariatric surgery
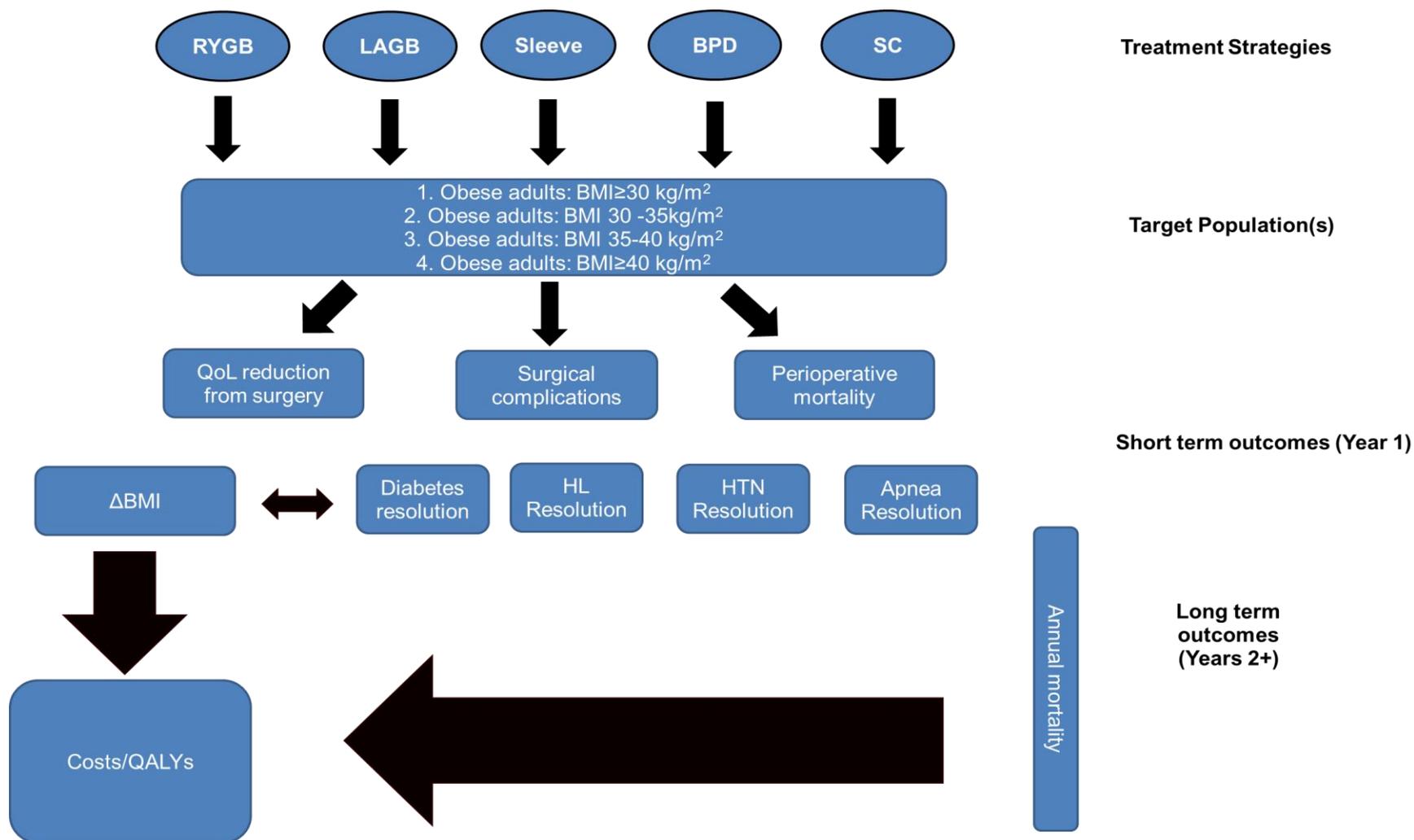
BMI = Body Mass Index; BPD/DS = Biliopancreatic Diversion/Duodenal Switch; HL = Hyperlipidemia; HTN = Hypertension; LAGB = Laparoscopic Adjustable Gastric Banding; QALY = Quality-Adjusted Life Year; QoL = Quality of Life; RYGB = Roux-en-Y Gastric Bypass; SC = Standard Care; Sleeve = Vertical Sleeve Gastrectomy

Table ES-6: Costs and consequences of bariatric surgery and nonsurgical standard care over 1 year of follow-up, among all patients with BMI>30

Outcome/Cost	Standard Care	RYGB	VSG	LAGB	BPD
BMI≥30					
Clinical Outcome					
BMI loss (mean)	1.44	10.4	9.76	7.76	12.48
Death (%)	1%	2%	2%	2%	2%
Reoperation (%)	0%	6%	3%	12%	7%
Medical complication (%)	0%	11%	13%	2%	21%
Diabetes resolution (%)	2%	14%	14%	13%	18%
Hypertension resolution (%)	4%	19%	23%	17%	19%
Hyperlipidemia resolution (%)	4%	23%	17%	9%	23%
Costs ($)					
Procedure	$3,710	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$787	$402	$1,478	$893
Other Complications	$0	$5,035	$5,167	$4,570	$5,925
TOTAL	$3,710	$30,099	$24,357	$22,035	$42,979
BMI 30-34.9					
Clinical Outcome					
BMI loss (mean)	1.17	8.45	7.93	6.305	10.14
Death (%)	1%	1%	1%	2%	2%
Reoperation (%)	0%	6%	3%	12%	7%
Medical complication (%)	0%	11%	13%	2%	21%
Diabetes resolution (%)	1%	10%	10%	9%	13%
Hypertension resolution (%)	3%	16%	20%	15%	16%
Hyperlipidemia resolution (%)	4%	22%	17%	8%	22%
Costs ($)					
Procedure	$3,042	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$787	$402	$1,478	$893

Outcome/Cost	Standard Care	RYGB	VSG	LAGB	BPD
Other Complications	$0	$4,274	$4,406	$3,809	$5,164
TOTAL	$3,042	$29,338	$23,596	$21,274	$42,218
BMI 35-39.9					
Clinical Outcome					
BMI loss (mean)	1.35	9.75	9.15	7.275	11.7
Death (%)	1%	2%	2%	2%	2%
Reoperation (%)	0%	6%	3%	12%	7%
Medical complication (%)	0%	11%	13%	2%	21%
Diabetes resolution (%)	2%	15%	15%	14%	20%
Hypertension resolution (%)	4%	20%	25%	18%	20%
Hyperlipidemia resolution (%)	4%	23%	18%	9%	23%
Costs ($)					
Procedure	$3,500	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$787	$402	$1,478	$893
Other Complications	$0	$4,845	$4,977	$4,380	$5,735
TOTAL	$3,500	$29,909	$24,167	$21,845	$42,789
BMI≥40					
Clinical Outcome					
BMI loss (mean)	1.62	11.7	10.98	8.73	14.04
Death (%)	1%	2%	2%	2%	3%
Reoperation (%)	0%	6%	3%	12%	7%
Medical complication (%)	0%	11%	13%	2%	21%
Diabetes resolution (%)	3%	23%	23%	21%	29%
Hypertension resolution (%)	5%	24%	30%	22%	24%
Hyperlipidemia resolution (%)	4%	23%	17%	9%	23%
Costs ($)					
Procedure	$4,269	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$787	$402	$1,478	$893

Outcome/Cost	Standard Care	RYGB	VSG	LAGB	BPD
Other Complications	$0	$5,820	$5,952	$5,356	$6,711
TOTAL	**$4,269**	**$30,884**	**$25,142**	**$22,820**	**$43,764**

BPD = biliopancreatic diversion; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; VSG = vertical sleeve gastrectomy.

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

Reference Case Analysis – Bariatric Surgery Versus Standard Care (10-year Time Frame)

In the 10 year time horizon analysis, bariatric surgery resulted in additional quality-adjusted life-years (QALYs) and increased costs compared with standard care (see **Table ES-7** on page ES-52). 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. However, in comparison to standard care, cost-effectiveness estimates are similar for all surgery types (ranging from $29,000 - $47,000 per QALY gained). Cost-effectiveness ratios were not calculated for VSG and LAGB in reference to RYGB (because they were less effective). The cost per QALY gained for BPD/DS was $77,574 in comparison to RYGB across all levels of BMI.

Table ES-7: 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	NA	NA
RYGB	$54,110	8.0807	$37,423	NA
VSG	$48,702	8.0417	$29,087	Less expensive & less effective
LAGB	$47,668	7.9252	$35,680	Less expensive & less effective
BPD	$65,741	8.2307	$46,508	$77,574
BMI 30-34.9				
Standard care	$27,943	7.9418	NA	NA
RYGB	$49,735	8.3529	$53,021	NA
VSG	$44,298	8.3211	$43,122	Less expensive & less effective
LAGB	$42,738	8.2273	$51,826	Less expensive & less effective
BPD	$61,410	8.4730	$63,011	$97,194
BMI 35-39.9				
Standard care	$32,538	7.6567	NA	NA
RYGB	$52,886	8.1351	$42,534	NA
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	NA	NA
RYGB	$58,257	7.8630	$30,995	NA
VSG	$53,047	7.8194	$23,784	Less expensive & less effective
LAGB	$52,255	7.6882	$29,552	Less expensive & less effective
BPD	$69,329	8.0322	$38,790	$65,431

BPD = Biliopancreatic Diversion; LAGB = Laparoscopic Adjustable Gastric Banding; RYGB = Roux-en-Y Gastric Bypass; VSG = Vertical Sleeve Gastrectomy.

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

In keeping with clinical results at one year of follow-up, cost-effectiveness values were most favorable in patients with a BMI of 40 or above. 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 more pronounced 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).

The results of sensitivity analyses are presented in detail in the full report. The model was robust to variance in a variety of assumptions regarding key estimates. For example, all procedures generated cost-effectiveness ratios <$100,000 even when an assumed all-cause mortality benefit was removed and also when all patients were assumed to regain all weight lost by five years post-surgery.

ICER Integrated Evidence Ratings

The ICER integrated evidence rating matrix is shown below; a detailed explanation of the methodology underpinning this rating system can be found in Appendix F to the full report. Separate ratings are provided for each of the populations and procedure comparisons under consideration; the ratings and rationale are described on the following pages.

Figure ES-10: ICER Integrated Evidence Ratings

Comparative Clinical Effectiveness	a High	b Reasonable/Comp	c Low
Superior: A	Aa	Ab	Ac
Incremental: B^+/B	B^+ a / Ba	B^+ b / Bb	B^+ c / Bc
Comparable: C^+/C	C^+ a / Ca	C^+ b / Cb	C^+ c / Cc
Inferior: D	Da	Db	Dc
Promising but Inconclusive: P/I	Pa	Pb	Pc
Insufficient: I	I	I	I

Comparative Value

Bariatric Surgery in Adults

1. Bariatric Surgery vs. Nonsurgical Management:

   a. B^+b (for BMI ≥35)

   b. Bb (for BMI 30-34.9 and type 2 diabetes)

   c. I (for BMI 30-34.9 and other comorbidities)

2. VSG vs. RYGB: Cb (for all BMI levels)

3. LAGB vs. RYGB: Db (for all BMI levels)

4. BPD/DS vs. RYGB: Bb (for all BMI levels)

Bariatric Surgery in Adolescents

1. Bariatric Surgery vs. Nonsurgical Management: Pb (for BMI ≥35)

2. VSG vs. RYGB: I

3. LAGB vs. RYGB: I

4. BPD/DS vs. RYGB: I

Bariatric Surgery in Children

INSUFFICIENT EVIDENCE FOR ALL COMPARISONS

Rationale for ICER Ratings

While the comparative evidence base has grown substantially for bariatric surgery in recent years, it is not without its major concerns. For one, there remain significant gaps in the understanding of the long-term course of patients following surgery; in particular, rates of weight recidivism and comorbidity relapse are poorly understood because of relatively high rates of loss to follow-up, due in part because of poor adherence with post-procedure support mechanisms by many. In addition, there is a lack of standardization in the methods used to report procedure-related complications, comorbidity resolution, and other key outcomes, making comparisons across studies problematic.

Nevertheless, we find the evidence comparing bariatric surgery to nonsurgical management in adults to be reasonably persuasive, in no small part because most lifestyle-based interventions have proved to be ineffective, regardless of intensity, population, or BMI level. The benefits of bariatric surgery with regard to shorter-term effects on BMI and comorbidities are consistently several-fold better than those of nonsurgical management among adults with BMI levels ≥35, which leads to our rating of "B+" (incremental or better). In addition, while not cost-saving, surgery appears to be a cost-effective alternative to nonsurgical management across a variety of studies, timeframes, and scenarios (including our own model), leading to a "b" rating (reasonable/comparable). Findings with respect to both clinical effectiveness and cost-effectiveness were similar among patients at lower BMI levels (30-34.9) who

were also diagnosed with type 2 diabetes; while interventions and study designs varied, weight-loss and diabetes resolution outcomes were consistent across these studies. We chose a "Bb" rating for these individuals, as the evidence base is not as mature in comparison to those at higher BMI levels. However, while patients in the diabetes studies also realized benefits in terms of other diabetes-related comorbidities such as hypertension and hyperlipidemia, little to no evidence was available on resolution of other comorbidities (e.g., sleep apnea, arthritis) for individuals at lower levels of BMI, leading to our "I" rating.

In comparing the individual procedures to each other, each has shown to reduce body weight and resolve key comorbidities in many; the true effects of numeric differences between procedures in weight loss and comorbidity resolution on mortality and long-term outcomes are not certain, however. Nonetheless, when comparing procedures across the domains of clinical effectiveness, harms, and cost to the common "gold standard" of gastric bypass, vertical sleeve gastrectomy appears to provide comparable clinical benefits at a slightly lower cost (leading to a Cb rating), laparoscopic adjustable gastric banding appears to be both less effective and less costly (leading to a Db rating), and biliopancreatic diversion is somewhat more effective and more costly than RYGB (leading to a Bb rating).

In contrast, the comparative evidence base in adolescents is truly emerging. We found only a single study comparing surgery to nonsurgical management in these patients. While this study was of good quality, it was small (N=50) and not complemented by any good- or fair-quality cohort studies. As such, we labeled the comparative clinical effectiveness to be "promising but inconclusive," and while we did not focus on adolescents in our economic model, felt that the incremental costs and effects in adolescents were likely to be of similar magnitude, leading to our Pb rating. This is restricted to individuals with a BMI ≥35, matching the entry criteria for the RCT.

The evidence was insufficient to make a determination regarding comparisons of individual procedures among adolescents due to limited or nonexistent comparative evidence. Similarly, we found no comparative studies involving these procedures performed in children less than 12 years of age.

1. Background

It is estimated that 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, hypertension, cardiovascular disease, high blood pressure, and sleep apnea. Obesity and its sequelae are estimated to generate $147 billion in health care costs in the U.S. 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, many of which have been shown to pose significant health risks of their own (National Institutes of Health, 2013). More recently, options for surgical intervention have 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 U.S. 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 laparoscopic approach. The choice of procedure primarily depends 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 also remission of certain obesity-related comorbidities (e.g., hypertension, diabetes). Long-term observational studies also suggest that bariatric surgery may also 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 (body mass index [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 FDA approved the use of a laparoscopic adjustable gastric banding device for use in patients with lower levels of obesity (BMI 30.0-34.9) and at least one obesity-linked condition (U.S. Food and Drug Administration, 2011).

As the use of these procedures has evolved over time, surgical approaches have also become more standardized and both pre- and post-operative support for patients has become more comprehensive. The American College of Surgeons (ACS) and American Society for Metabolic and Bariatric Surgery (ASMBS) have developed joint criteria for accreditation of bariatric facilities (ACS/ASMBS, 2014). Standards for different levels of facilities are described, and involve 1) case volume and patient/procedure selection; 2) quality measures; 3) equipment and instrumentation; 4) critical care support; 5) patient education as well as short- and long-term follow-up; 6) data collection; and 7) accreditation in specific populations (e.g., adolescents). Similar standards for "centers of excellence" have been produced by organizations created to address standardization within particular surgical specialties (e.g., Surgical Review Corp.).

Clinical interest in expanding the use of bariatric surgery to a broader set of individuals remains high. 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 of 1,136 long-term studies (2.6%) 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. For example, a 5-year follow-up study after gastric bypass surgery documented an average regain of 80% of the body mass index (BMI) lost following surgery (Magro, 2008); nearly 20% of patients with a pre-operative BMI >40 had failed to achieve the required reductions in excess body weight by year 4 of follow-up, double the rate observed at year 2. Other studies have documented more modest weight regain levels; however, the lack of consistent long-term data is problematic for understanding the true trajectory of weight following bariatric surgery.

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 U.S. (American Society for Metabolic and Bariatric Surgery, 2014). Also, as with any surgical procedure, there are general surgical risks, including hemorrhage, wound infection, deep vein thrombosis and/or pulmonary embolism, and anesthesia reactions (Mayo Clinic, 2014).

Policy Context

About 93 million Americans are classified as obese (Obesity Action Coalition, 2014). While the number of obese individuals has remained stable in recent years, obesity continues to be one of the most prevalent public health issues in the U.S. (Ogden, 2014). In June 2012, the American Medical Association officially recognized obesity as a chronic disease, believing it would more effectively address the issue; however, the new classification remains controversial among advocates, policymakers, and the medical community, who feel that such a designation may distance patients from responsibility for their condition (Pollack, 2013).

Compounding the problem is the lack of viable treatment alternatives. Success rates from lifestyle modifications alone have been modest at best, and the risk-benefit tradeoffs for weight-loss medications are questionable. Clinical interest in expanding the use of bariatric surgery is therefore justifiably high, but there are uncertainties regarding the relative performance of each type of procedure in specific patient populations (e.g., adult versus pediatric patients, moderately versus severely/moderately obese, etc.).

As the Washington State Health Care Authority reviews its coverage policy for bariatric surgery, it is therefore timely to assess the evidence on the clinical benefits and cost-effectiveness of common weight loss procedures across all relevant populations, including those defined by level of obesity, age, and presence of specific types of comorbidity.

2. Alternative Treatment Strategies

Roux-en-Y Gastric Bypass (RYGB)

Roux-en-Y gastric bypass (RYGB) is the most commonly performed bariatric procedure worldwide (ASMBS).   RYGB can be performed laparoscopically, robotically, or openly and has a typical duration that ranges from 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 is intended to restrict food intake and promote satiety after small amounts are consumed (University of Illinois Bariatric Surgery Program).

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 is comprised of 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. In addition to potential complications, RYGB has a few disadvantages, including the irreversibility of the procedure and its impedance on a patient's ability to absorb nutrients. Patients will need to take nutrient supplements for the remainder of their lives and monitor their intake of carbohydrates to avoid gastric discomfort, vomiting and diarrhea.

Biliopancreatic Diversion/Duodenal Switch (BPD/DS)

Biliopancreatic diversion is commonly performed on so-called "super-obese" individuals--those with a BMI of 50 kg/m2 or greater (Mayo Clinic). Similar to sleeve gastrectomy, 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 which 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 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.

Patients typically remain in the hospital for four to seven nights after BPD and take three to four weeks to recover. Because BPD/DS is a malabsorptive procedure, patients are at risk of developing nutrient deficiencies and will need 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 3-4 loose bowel movements a day. Nutrient deficiency conditions such as night blindness, iron deficiency anemia, beriberi, osteoporosis, and protein energy malnutrition may also occur.

Figure 2: Biliopancreatic Diversion/Duodenal Switch

Source: http://asmbs.org/patients/bariatric-surgery-procedures
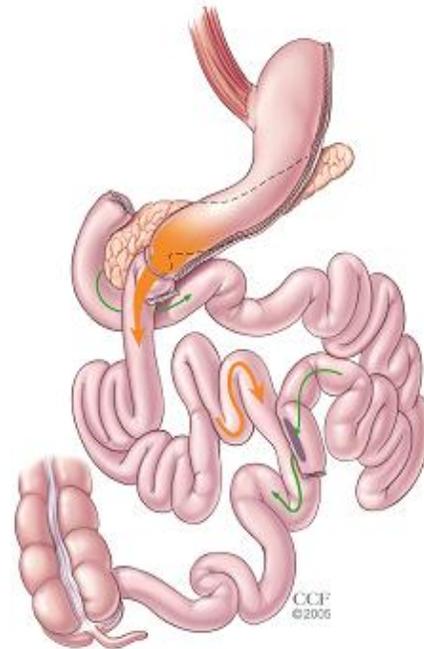
Figure 3: Laparoscopic Adjustable Gastric Banding
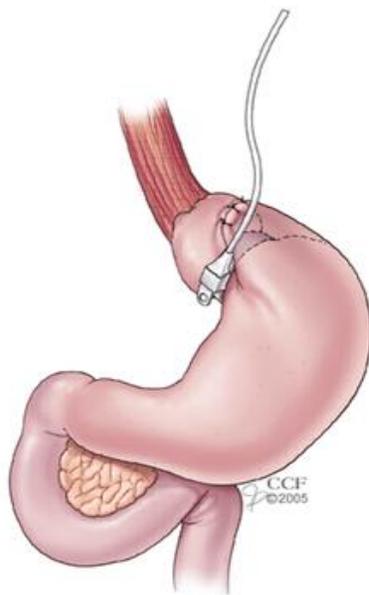
Source: http://asmbs.org/patients/bariatric-surgery-procedures

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 by means of 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 isn't too physically taxing, and are usually fully recovered within 1-2 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 are

infrequent but can include hemorrhage, port infection, band infection, obstruction, nausea, vomiting, band erosion into the stomach, esophageal dilation, and inadequate weight loss.

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 risk for complications related to a longer procedure, have an excessively large liver, or have extensive scar tissue are considered possible candidates for sleeve gastrectomy (Cleveland Clinic, 2015). Once weight loss occurs, the liver decreases in size and the risk of surgery-related complications reduces. Patients may then return to the hospital to undergo gastric bypass as a second stage procedure.

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 1-2 weeks. VSG is not a malabsorptive procedure so there is less risk of nutrient deficiencies postoperatively. Potential complications include bleeding, infection, injury to other organs, conversion to an open procedure, and leakage from the staple line that divides the stomach (Cleveland Clinic, 2015).

Emerging Technologies and Procedures

EnteroMedics V-Bloc® /Maestro System®

The newly FDA-approved Maestro system is an implant that generates an intermittent electrical pulse that blocks the vagus nerve, the primary nerve regulating the digestive system. By blocking these nerve signals, the implant reduces feelings of hunger and promotes earlier feelings of fullness. The device has been approved for adults with a BMI of 40 to 45 kg/m2 or a BMI of 35 and greater accompanied by at least one other obesity-related comorbidity. In a recent clinical trial of 239 patients randomized to receive either the Vagal Nerve Block or a sham device (mean age 47, 84% female, mean BMI 41 kg/m^2), 52.5% of patients who received V-BLOC therapy lost 20% or more of their excess weight in 12 months (Ikramuddin, 2014). Similar devices include IntraPace's Abiliti®, Metacure's DIAMOND® (Tantalus), and Medtronic Transcend®. All devices operate by sending electronic stimulation to the stomach but have had disappointing results in clinical trials.

EndoBarrier®

The EndoBarrier functions similarly to RYGB without involving invasive surgery. The procedure can be 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).

Several prospective studies have found that the device helps decrease HbA1c levels and improve cholesterol, blood sugar, and triglycerides (Escalona, 2012; de Jonge, 2013; Schouten, 2010). Average excess weight loss has been approximately 19% (Schouten, 2010). The device has not yet been approved by the FDA and is currently being investigated in the "ENDO Trial" in a multiple centers across the United States.

Intragastric Balloons
There are several intragastric balloons in use today. The BioEnterics® Intragastric Balloon (BIB® or "Orbera"), the Silimed® Intragastric Balloon ("BIS"), the Spatz3 Adjustable Balloon System, and the ReShape Medical® Intragastric balloon are saline balloons. In addition, there is the Helioscopie Heliosphere® Bag System which is an air based bag or balloon. These balloons have been used as pre-operative procedures as well as primary bariatric procedures in multiple trials, although there is not yet an FDA approved balloon in use in the United States.

The balloons are inserted in the stomach via endoscopy and filled with air or water. By occupying space in the stomach, patients feel full sooner and eat smaller portion sizes. In the recent REDUCE pivotal trial of the ReShape balloon (n=326; mean age 44 years, 95% female, mean BMI 35 kg/m^2) 55% of patients lost on average 25.1% of excess weight within six months compared to patients participating in diet and exercise treatment (11.3%, p=0.004) (Ponce, 2014).

Vibrynt Prevail Implant System
The Vibrynt Prevail® Implant System is an investigational device in the U.S. that is designed to limit food consumption by restricting the stomach's ability to expand. The device is inserted laparoscopically through a single incision on top of the stomach and positioned within the ribcage. It is then inflated with sterile saline solution. Similar to LAGB, the amount of restriction of the implant can be altered through an adjustment port and is completely reversible.

Laparoscopic Gastric Plication
Laparoscopic gastric plication is a minimally invasive weight-loss surgery that reduces the size of the stomach to approximately three ounces. The procedure involves sewing one or more large folds in the stomach without cutting, stapling, rerouting, or removing part of the stomach or intestines.

The hospital stay is typically 24 - 48 hours. Recovery times may vary, but patients can generally resume normal activities within seven to 10 days. Gastric plication can be combined with the laparoscopic adjustable gastric band. When performed together, these procedures create a small stomach pouch at the top of the stomach and a narrow, sleeve-shaped lower stomach that cannot expand. This results in rapid early weight loss seen from plication, and the ability to further sustain weight loss over a longer period of time with the adjustable gastric band (Doctors of Weight Loss, 2015). Limited published evidence on the procedure is available, and it is not currently covered by major insurers.

3. Clinical Guidelines and Training Standards

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

http://content.onlinejacc.org

The AHA/ACC/TOS joint guidelines suggest that bariatric surgery is an appropriate option for patients with a BMI of at least 40kg/m^2, or with a BMI of at least 35kg/m^2 accompanied by an obesity-related comorbid condition. Surgical candidates must be motivated to lose weight, but have not experienced weight loss sufficient to achieve target health outcomes despite participation in behavioral treatment, with or without the addition of pharmacotherapy. AHA/ACC/TOS guidelines do not provide a preference on the type of bariatric procedure used, and instead suggest that choice of procedure should be based on patient factors such as age, severity of obesity, comorbid conditions, surgical risk factors, risk for short- and long-term complications, and behavioral and psychosocial factors. Guidelines suggest that evidence is insufficient to support the use of bariatric procedures in patients with a BMI less than 35kg/m^2.

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

https://www.aace.com

Bariatric surgery should be considered for patients with a BMI $\geq$40kg/m^2 who do not have existing medical complications and for whom surgery would not pose excessive risk. Patients with a BMI $\geq$35kg/m^2 who have at least one comorbid condition, such as type 2 diabetes, hypertension, hyperlipidemia, or obstructive sleep apnea may also be eligible. Patients with a BMI between 30 and 34.9kg/m^2 with comorbid diabetes or metabolic syndrome may be eligible, though there is less evidence on the effects of bariatric surgery in this patient population. Evidence is considered insufficient to recommend any bariatric procedure for glycemic control alone.

AACE/TOS/ASMBS guidelines state that evidence is currently insufficient to recommend one procedure over another, and suggest that procedure type should be based on individual goals, available regional expertise, patient preferences, and personalized risk stratification. Laparoscopic procedures are generally preferred over open ones. LAGB, LSG, RYGB, and BPD$\pm$DS are considered to be the primary procedures of interest, though the guidelines express concerns regarding greater risks of nutritional deficiency associated with BPD$\pm$DS.

U.S. Department of Veteran's Affairs/Department of Defense (VA/DoD) (2014)

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

Bariatric surgery should be offered in conjunction with lifestyle modification as an option for weight loss in adults with a BMI greater than 40kg/m^2 or with a BMI of 35.0-39.9kg/m^2 accompanied by one or more obesity-related comorbid conditions. Surgery can also be considered for improvement of obesity-related conditions aside from weight loss in some patients with a BMI over 35kg/m^2. Current evidence is insufficient to support the use of bariatric surgery for weight loss or to improve comorbid conditions in patients over the age of 65 or with a BMI less than 35kg/m^2. Patients who are candidates for bariatric surgery should be well-informed of the benefits and possible risks associated with the procedure. A consultation with a bariatric surgical team prior to surgery should be offered to patients who request more information. Following surgery, patients should be provided with lifelong follow-up services to

Original NIH-based Criteria

Criteria originally promulgated by the U.S. National Institutes of Health are often cited in other clinical guidelines and payer coverage policies, despite their age. They are summarized here for completeness.

National Heart, Lung, and Blood Institute (1998)

http://www.nhlbi.nih.gov

Bariatric surgery is an option for weight loss in patients with severe obesity, characterized by a BMI $\geq$40kg/m^2 or $\geq$35kg/m^2 with comorbid conditions such as cardiovascular complications, sleep apnea, uncontrolled type 2 diabetes, or physical limitations that interfere with daily activities, in whom other methods of weight loss have failed and who are at high risk for obesity-related morbidity and mortality. Patients undergoing surgical intervention should be cared for by a multidisciplinary team that includes medical, behavioral, and nutritional components. Support should be available in each of these areas both before and after the procedure. Following surgery, patients should receive lifelong follow-up to monitor for vitamin deficiencies, gastrointestinal complications, or mood changes.

Guidelines for Pediatric Surgery

Clinical guidelines published regarding the use of bariatric procedures specifically in children are summarized below.

Endocrine Society (2007)

http://press.endocrine.org

For the treatment of obesity in children, the Endocrine Society recommends bariatric surgery for adolescents with a BMI above 50 kg/m^2, or with a BMI above 40kg/m^2 with severe comorbid conditions in whom lifestyle modifications, with or without the use of pharmacotherapy, have been unsuccessful. Qualified adolescents and their families must be psychologically stable and able to adhere to lifestyle changes. Families must have access to experienced bariatric surgeons and multidisciplinary teams able to assess the benefits and risks of surgery.

Selected ex-U.S. Guidelines

Guidelines published by the U.K.'s National Institute for Health and Care Excellence (NICE) as well as the Canadian Medical Association are also summarized below.

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

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

Bariatric surgery can be considered for treatment of obesity in patients with BMI $\geq$40kg/m^2 or $\geq$35kg/m^2 with severe comorbid conditions, such as type 2 diabetes or high blood pressure who meet the following criteria:
- Health and/or comorbidity would be improved with weight loss;
- Attempts at all appropriate non-surgical methods of weight loss have been made without adequate results;
- Have been receiving or will receive intensive medical management;

- Are suitable candidates for anesthesia and surgery; and
- Are able to commit to long-term follow-up.

Bariatric surgery is also recommended for patients with a BMI >50kg/m^2 in whom other interventions have not been effective. Expedited surgical assessment may be considered for patients with BMI $\geq$35kg.m^2 with recent-onset type 2 diabetes. Patients with BMI between 30 and 34.9kg/m^2 with recent-onset type 2 diabetes, as well as patients of Asian descent with recent-onset type 2 diabetes and a BMI below this range, may also be assessed for surgery.

Surgery is generally not recommended for children, but may be considered in exceptional circumstances in patients who have reached physiological maturity. Pediatric patients should be cared for by multidisciplinary teams with pediatric expertise. Pediatric patients should undergo psychological, educational, family, and social assessments before qualifying for surgery. They should also undergo a medical screening including genetic testing for rare but treatable causes of obesity.

Canadian Medical Association (2007)

http://www.cmaj.ca
Bariatric surgery is suggested for adults with clinically severe obesity, characterized by a BMI of $\geq$40kg/m^2 or $\geq$35kg/m^2 with severe comorbid conditions, in whom lifestyle intervention has not been adequate to reduce weight. In adolescents, surgery should be reserved for special cases and should be performed by experienced teams. When possible, a minimally invasive technique is recommended for all bariatric procedures. Recommended surgical options include vertical banded gastroplasty, LAGB, BPD$\pm$DS and RYGB. Care teams for bariatric patients should include a dietician, an internist, an anesthetist, a psychiatrist or psychologist, nurses, a respiratory physician, a physiotherapist and a social worker.

4. Medicare and Representative Private Insurer Coverage Policies

4.1 Centers for Medicare and Medicaid Services (CMS)

http://www.cms.gov/medicare

A 2009 national coverage decision (NCD) on coverage for bariatric surgery provides coverage for RYGB, BPD with DS, and LAGB for beneficiaries who meet the following criteria:

- BMI ≥ 35
- One or more obesity-related comorbidities
- Failed prior medical treatment for obesity

The NCD specifically states that type 2 diabetes should be considered a comorbidity for purposes of coverage, but makes no specific mention of any other obesity-related comorbidities.

Open adjustable gastric banding and open VSG are non-covered procedures. CMS allows Medicare Administrative Contractors (MACs) to make local coverage decisions (LCDs) on stand-alone laparoscopic VSG. Noridian Healthcare Solution's LCD for Washington covers laparoscopic VSG if patients meet the above three clinical criteria and are _younger_ than age 65, as the evidence base to support VSG is felt to be too weak in older patients.

4.2 Representative National Private Insurer Policies

Aetna

http://www.aetna.com

Aetna covers RYGB, VSG, BPD (w/ or w/o DS) and LAGB for adults with a BMI > 40, or with a BMI > 35 with severe comorbidities, defined as:

- Clinically significant obstructive sleep apnea
- Coronary heart disease
- Medically refractory hypertension
- Type 2 diabetes

The same procedures are covered for adolescents who have completed bone growth and meet one of the following criteria:

- BMI > 40 and clinically significant obstructive sleep apnea, type 2 diabetes mellitus, or pseudotumor comorbidities
- BMI > 50 with less serious comorbidities (e.g., impairment in completing daily life activities, psychosocial distress resulting from obesity, gastroesophageal reflux disease)

All bariatric surgery candidates must have attempted and been unsuccessful with prior weight loss regimens, and complete either a physician-supervised nutrition and exercise program or a multi-disciplinary surgery preparatory regimen for at least six out of the past 24 months prior to the surgery. LAGB revision of RYBG or VSG is considered experimental and investigational, as are any bariatric surgery to treat idiopathic intracranial hypertension or infertility, gastric bypass to treat gastroparesis, and RYGB to treat gastroesophageal reflux in non-obese patients.

CIGNA

https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies

CIGNA covers RYGB, VSG, and LAGB for adults and adolescents who have completed bone growth with a BMI ≥ 40, or with a BMI ≥ 35 and clinically significant comorbidities related to obesity including type 2 diabetes, coronary artery disease, mechanical arthritis in a weight-bearing joint, and poorly controlled or pulmonary hypertension. BPD/DS is covered only for patients whose BMI exceeds 50. CIGNA does not cover simultaneous RYBG and gastric banding BPD without a duodenal switch, and does not cover bariatric surgery for the treatment of type 2 diabetes mellitus alone.

All candidates for bariatric surgery must participate in a medical weight-management program supervised by a physician or registered dietician for at least three consecutive months of the past year. CIGNA requires recommendations for surgery from a bariatric surgeon and one other physician, in addition to clearance from a mental health provider and a nutritional evaluation from a physician or registered dietician.

Gastric banding adjustments are covered when performed to control the rate of weight loss and/or to treat other symptoms resulting from gastric banding. CIGNA covers surgical reversal in cases of stricture or obstruction resulting from the original surgery.

Humana

http://apps.humana.com

Humana covers RYGB, BPD (w/ or w/o DS), VSG, and LAGB. To be eligible for bariatric surgery, patients must have a BMI > 40, or a BMI > 35 with hypertension, joint disease, life-threatening cardiopulmonary problems, or type 2 diabetes. Patients must also have been unsuccessful with previous medical treatment for obesity and be psychologically cleared for surgery. Psychological clearance is used to exclude patients who cannot provide informed consent or who are unable to follow pre- or post-operative regimens.

Patients are eligible for repeat bariatric surgery to correct complications resulting from the initial surgery, and in the event of inadequate weight loss despite adherence to post-operative regimen. Humana does not cover repeat surgery if the stomach pouch created by bariatric surgery stretches due to overeating.

United HealthCare

https://www.unitedhealthcareonline.com

United HealthCare covers RYGB, BPD (with or without DS), VSG, and LAGB. These procedures are considered to be medically necessary treatments for weight loss in adult patients with a BMI > 40, or with a BMI > 35 with at least one of the following comorbidities: type 2 diabetes, cardiovascular disease, hypertension with blood pressure greater than 140/90 despite pharmacotherapy, a history of coronary artery disease with surgical intervention, sleep apnea, other cardiopulmonary problems, or a history of cardiomyopathy. The patient must also show documented attempts to lose weight through a structured diet program that includes provider notes or weight loss logs from a program for at least six months.

Patients must have completed a psychological evaluation to rule out major mental health disorders that could interfere with compliance and follow-up requirements after surgery. United HealthCare covers bariatric procedures for adolescents if the adolescent patient has reached greater than 95% of

estimated adult height based on overall growth pattern, has a Tanner stage of at least 4 (a level of near-adult development on the Tanner scale), and meets all other adult criteria for surgery. The procedures are not considered medically necessary in patients that have not yet reached physical maturation due to a lack of research on potential safety issues and long-term effects in this age group.

Bariatric surgery is not considered medically necessary for conditions other than obesity. Bariatric procedures other than those defined above are not considered to be medically necessary. Reoperation for a prior procedure is considered to be medically necessary for complications associated with the original surgery, including stricture, obstruction, pouch dilation, erosion, or band slippage when the complication leads to abdominal pain, inability to eat or drink, or vomiting.

WellPoint/Anthem

http://www.anthem.com/medicalpolicies/policies
Wellpoint/Anthem considers RYGB, LAGB, BPD/DS, and VSG medically necessary in patients with a BMI ≥ 40, or with a BMI ≥ 35 with one or more obesity-related comorbidities, such as type 2 diabetes, cardiovascular disease, hypertension, or cardio-pulmonary problems (e.g., sleep apnea). Bariatric procedures other than those listed above, including BPD without duodenal switch, are considered investigational and are not covered. Bariatric surgeons with experience in pediatric populations may request special consideration for patients under 18 years old with severe morbid obesity and unique circumstances.

To qualify, the patient must have participated in a physician-evaluated non-surgical method of weight reduction. The requesting physicians must confirm that the patient is able to understand and comply with all phases of care of follow-up requirements, has had post-surgical expectations assessed, has undergone both medical and mental health evaluation and deemed an acceptable surgical candidate, has received an explanation of risks, benefits, and uncertainties, and has a treatment plan that includes dietary evaluations and counseling in nutrition, exercise, psychological issues, and has supportive resources available as needed.

Surgical repair following the procedure is medically necessary with documentation of a complication related to the original surgery, such as fistula, obstruction, erosion, disruption or leakage of a suture/staple line, band herniation, or pouch enlargement due to vomiting. A repeat surgery or conversion to another method may be medically necessary in cases where the patient continues to meet all criteria for bariatric surgery, has documented compliance with previous postoperative diet and exercise program, and has experienced weight loss less than 50% of pre-operative excess weight with weight remaining at least 30% over ideal body weight 2 years after the original surgery. Reoperation is not medically necessary in cases of stretching of the stomach pouch due to overeating.

4.3 Representative Regional Private Insurer Policies

Health Net

https://www.healthnet.com/portal/provider/
Health Net covers laparoscopic VSG and open or laparoscopic RYGB for adult patients who have been 1) morbidly obese for more than two years and have a BMI ≥ 40; or with a BMI ≥ 35 and an obesity-related comorbidity including (but not limited to) type 2 diabetes, severe coronary artery disease, hypertension, and severe joint or spine pain or motion limitation from degenerative osteoarthritis. The same

procedures are covered for physiologically mature adolescents older than 13 with a BMI ≥ 40 with serious comorbidities related to obesity (such as type 2 diabetes or benign intracranial hypertension), or with a BMI ≥ 50 with less serious comorbidities (such as hypertension, weight related arthropathies, gastroesophageal reflux, or severe psychosocial distress).

Health Net covers additional bariatric surgical procedures with restrictions. Open or laparoscopic BPD/DS is restricted to patients with a BMI > 50 who will receive a common channel >100 cm. Open or laparoscopic RYGB with long limb (between 100 and 200 cm) is limited to patients with BMI > 50. In high-risk patients, laparoscopic VSG may only be used as a primary surgery as part of a "planned staged approach." The coverage policy notes that laparoscopic surgeries are contraindicated in patients with BMI > 70 or hepatomegaly. Health Net considers LAGB for patients with BMI between 30 and 35 investigational regardless of the presence or absence of comorbidities. Health Net considers BPD without duodenal switch not medically necessary.

All candidates for bariatric surgery must have attempted weight loss in the past without success. Adult patients must be evaluated and cleared by a licensed mental health care professional experienced in weight-loss surgery issues, and all patients must have not had an alcohol or substance abuse problem during the past year. Adolescent patients are also required to avoid pregnancy for one year post-surgery.

Repeat, revision, or conversion surgery may be covered in the presence of technical failure of the original procedure or if the initial procedure results in inadequate weight loss. In both circumstances, patients are required to have followed post-operative diet and exercise regimens.

Premera Blue Cross

https://www.premera.com/medicalpolicies/CMI_003698.htm
Premera Blue Cross covers RYGB, VSG, BPD/DS, and LAGB for patients with a BMI > 40, or BMI > 35 accompanied by at least one of the following weight related comorbidities: established coronary artery disease (history of myocardial infarction, angina pectoris, coronary artery surgery, or angioplasty), other atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, or blood pressure greater than 140/90 despite medical intervention), a diagnosis of type 2 diabetes that is uncontrolled by pharmacotherapy, or moderate to severe sleep apnea. Other procedures, including BPD without DS, are considered to be investigational and not medically necessary. Patients younger than 18 years old may be considered for a bariatric procedure with BMI > 40 and serious obesity-related comorbidities, or with BMI > 50 and less severe comorbidities.

Patients must have participated in a physician supervised weight loss program lasting at least six consecutive months within the two years preceding surgery. Patients must also complete a psychological evaluation with a licensed mental health provider to assess emotional stability and ability to comply with post-surgical limitations.

Gastric banding is not recommended for patients with BMI > 50, as it is associated with less weight loss than other procedures in this patient population. Patients may be eligible for revisionary surgery to address peri- or postoperative complications. Patients who do not achieve adequate weight loss following adjustable gastric banding must show compliance with post-surgical diet and follow-up appointments in order to be considered for a second procedure.

The Regence Group

http://blue.regence.com

The Regence Group covers LAGB, RYGB, and VSG. BPD, with or without DS, is considered an investigational procedure and is not currently covered. Covered procedures are considered medically necessary in adults who have a BMI ≥ 40, as well as in those with a BMI ≥ 35 accompanied by type 2 diabetes or two of the following: hypertension, dyslipidemia, coronary artery disease, or sleep apnea, all of which must be documented to be refractory to previous medical management. Use of these procedures in any patient not meeting the above criteria is considered investigational and not covered.

Patients must have participated in a medically directed weight loss program for at least six months within the 24 months prior to surgery. Patients must also complete a psychological assessment and have a documented absence of any psychological condition that may limit their ability to comply with post-operative instructions, such as substance abuse, eating disorders, schizophrenia, borderline personality disorder, or uncontrolled depression.

Reoperation to remove an adjustable gastric band in favor of RYGB or VSG is considered medically necessary if all aforementioned criteria for bariatric procedures continue to be met during the period following placement of the gastric band. Reoperation is considered medically necessary for surgical complications including band erosion or slippage that cannot otherwise be adjusted, leak, obstruction, staple-line failure, insufficient weight loss. Reoperation is considered not medically necessary in cases of early satiety, nausea, patient dissatisfaction, reflux, or conversion of a prior procedure to a different procedure.

5. Previous Health Technology Assessments and Systematic Reviews

We were able to identify seven formal health technology assessments evaluating at least one of the four bariatric surgery procedures of interest for this review, two of which compared surgical interventions individually and collectively against conventional weight-loss treatments, including one in a pediatric population. We also found three systematic reviews comparing multiple bariatric procedures directly, and one comparing bariatric surgery to nonsurgical management.

5.1 Health Technology Assessments

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 insufficient for comparing the outcomes of multiple procedures directly. There is also a low strength of evidence for adverse events 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 which 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 gastric bypass, the data is 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 adverse events, 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 RCTs are lacking, 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. Moreover, the results suggest that both a high procedure volume and extensive surgical experience are associated with better clinical outcomes.

California Technology Assessment Forum (CTAF, 2009)

http://www.ctaf.org/reports/laparoscopic-adjustable-silicone-gastric-banding-obesity
In an evidence review focused on the effectiveness of LAGB to treat obesity, data suggest RYGB is more effective at improving weight outcomes and resolving comorbidities, though the evidence for the latter is less robust. 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. When performed at experienced centers, both procedures have acceptable rates of morbidity and mortality. The type of patient that would receive the greatest benefit from either procedure is unclear, but LAGB should remain an option for those who are given appropriate informed consent about the benefits and harms of LAGB relative to RYGB.

California Technology Assessment Forum (CTAF, 2010)

http://www.ctaf.org/reports/sleeve-gastrectomy-stand-alone-bariatric-procedure-obesity
Another evidence review by CTAF assessed the use of VSG as a stand-alone procedure for the surgical treatment of obesity. Because VSG is a less-invasive procedure with fewer complications, it may be an attractive option for the morbidly obese. Several case series and retrospective studies, along with two small RCTs, suggest that VSG is results in significant excess weight loss, but longer-term outcomes are uncertain.

California Technology Assessment Forum (CTAF, 2012)

http://www.ctaf.org/reports/bariatric-surgery-treatment-type-2-diabetes-mellitus
Yet another evidence review by CTAF evaluated the use of bariatric surgery for the treatment of type 2 diabetes in obese patients. Studies show that the remission rate ranged from 60% with LAGB to 100% with BPD, and significantly more patients achieve resolution after bariatric surgery than with those receiving 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.

Washington State Health Care Authority (HCA, 2007)

http://www.hca.wa.gov/hta/Pages/pbs.aspx
A health technology assessment conducted by the ECRI Institute for the Washington State HCA found limited evidence on outcomes of bariatric surgery procedures in morbidly obese adolescent patients. The available evidence does suggest, however, that both LAGB and RYGB are associated with significant weight loss compared to nonsurgical approaches. Additional benefits of surgery include remission of both hypertension following either LAGB or RYGB, and type 2 diabetes following LAGB, though the strength of evidence on resolution of any comorbidity is poor. There were a number of complications associated both procedures, including mostly band-and port-associated complications with LAGB and several minor and major complications related to RYGB. Variations in outcomes according to patient characteristics were unclear based on the available literature. To assess costs, an analysis of publically available data was conducted, but the evidence was insufficient to determine overall cost-effectiveness of surgery compared to conventional treatments.

5.2 Systematic Reviews

Buchwald 2004

Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292(14):1724-1737.
http://jama.jamanetwork.com.ezp-prod1.hul.harvard.edu/article.aspx?articleid=199587
A systematic review and meta-analysis evaluated 136 studies comparing the effectiveness and safety of bariatric surgery procedures for impact on weight loss, mortality, and obesity-related comorbidities (i.e., diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea). The overall treatment effect for excess weight loss was 61.2% for all procedures; patients undergoing LAGB, RYGB, VSG, and BPD (with or with DS) had a mean excess weight loss of 47.5%, 61.6%, 68.2%, and 70.1%, respectively. Perioperative mortality ranged from 0.1% to 1.1%. All comorbid conditions either improved or were resolved in at least 62% of patients across all procedures.

Colquitt 2014

Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. *Cochrane Database Syst Rev*. 2014;8:CD003641.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003641.pub4/abstract
A systematic review and meta-analysis of 22 RCTs conducted by the Cochrane Collaboration found that bariatric surgery is associated with greater improvements in weight loss outcomes and comorbidities for all procedures (LAGB, RYGB, BPD with DS, VSG, and VSG with duodenojejunal bypass) compared to nonsurgical treatments. Both RYGB and VSG produced greater weight reductions than LAGB, with comparable efficacy between them, and BPD/DS was associated with the greatest weight loss. Adverse events, including reoperations, were poorly reported and most studies were of short duration (1 to 2 years) so the long-term impact of surgery is unclear. There is a lack of evidence for resolution of comorbidities in people who do not meet the current standards for undergoing bariatric surgery.

Chang 2013

Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery an updated systematic review and meta-analysis, 2003-2012. *JAMA Surg*. 2014;149(3):275-287.
http://archsurg.jamanetwork.com.ezp-prod1.hul.harvard.edu/article.aspx?articleid=1790378
Chang and colleagues published a systematic review and meta-analysis of 164 studies evaluating the effectiveness and safety of bariatric surgery; meta-analyses for RCTs and observational studies were conducted separately. Perioperative and postoperative mortality rates were low in both RCT and observational study analyses, with the lowest mortality rate associated with LAGB. Complications were lower in observational studies compared with RCTs, with the lowest rates for VSG and LAGB. However, reoperation rates were the lowest with RYGB and highest with LAGB in both RCT and observational study evaluations. Across the RCTs, excess weight loss increased in years one and two following surgery, but declined in year three. Similarly, observational studies showed that excess weight loss increased between years one and two, but there was no change between years two and three. For comorbidity outcomes, all procedures were associated with significant improvements.

6. Ongoing Clinical Trials

Table 1: Ongoing Clinical Trials

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Gastric bypass					
Effect of Long Biliopancreatic Limb RYBG on Weight Loss and Comorbidities (Elegance) NCT 01686997	RCT	RYGB 75cm limb RYGB 150cm limb Primary and repeat surgery	N = 280 Age 18 – 65 Men and women BMI > 40 or BMI > 35 with comorbidity All BMI levels accepted in case of repeat surgery	Weight reduction Secondary Outcomes: • Decrease in comorbidities • QOL • Complications • Reoperations	December 2018
Calorie Reduction Or Surgery: Seeking Remission for Obesity and Diabetes (CROSSROADS) NCT01295229	RCT	RYGB Lifestyle intervention	N = 40 Age 25 – 65 Men and women BMI 30 – 40 No malignant tumors, cirrhosis, HIV, or serious mental illness No prior bariatric or GI surgery, or major organ transplant between 1995 and 2010	Feasibility of methods Diabetes remission Secondary Outcomes: • Efficacy of intervention	June 2015
DSS: Diabetes Surgery	RCT	Intensive medical	N = 120	HbA1c < 7.0%	March 2017

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Study – Intensive Medical Management of Type 2 Diabetes, With and Without Gastric Bypass Surgery NCT00641251		management RYBG and intensive medical management	Age 30 – 67 Men and women BMI 30 – 39.9 T2D for > 6 months with HbA1c > 8.0% No cardiovascular events within past six months No cardiovascular disease No cancer unless disease-free for five years No significant anemia	Systolic blood pressure < 130 mm Hg LDL cholesterol < 100 mg/dl	
Gastric Banding					
HERO Study: Helping Evaluate Reduction in Obesity NCT00953173	Obs. Cohort	LAGB (LAP-BAND AP)	N = 1,106 Age > 18 Men and women BMI > 40, BMI > 35 with comorbidity, or weight 100lb over ideal No prior bariatric surgery No type 1 diabetes	Change in weight, waist and hip circumference Change in concomitant medication use Change in health-related quality of life	March 2016
Multiple Procedures					
Surgical Treatment for Morbid Obesity by Sleeve Gastrectomy Versus Gastric Bypass (SLEEVE) NCT00722995	Obs. Cohort	Sleeve Gastrectomy Gastric Bypass	N = 280 Age 18 – 60 Men and women BMI > 40 or > 35 with comorbidities	Composite criteria of morbidity/mortality Secondary Outcomes • Frequency of morbid events	March 2015

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
				• % excess weight loss • Regression of morbidities • QOL	
Comparison of Laparoscopic Sleeve Gastrectomy and Roux-Y-gastric bypass in the Treatment of Morbid Obesity NCT00356213	RCT	Sleeve Gastrectomy Gastric Bypass	N = 200 Age 18 – 60 Men and women BMI > 40	Effectiveness in terms of weight loss Reduction of comorbidity QOL	August 2016
Outcomes Comparison Between Gastric Band, Laparoscopic Sleeve Gastrectomy and Gastric Bypass Surgeries in Obese Adolescents NCT02004561	Obs. cohort	Gastric Band Laparoscopic Sleeve Gastrectomy Gastric Bypass	N = 26 Age 14 – 19 Men and women BMI > 40 or BMI > 35 with comorbidities Physically or nearly physically mature No uncontrolled mental health or substance abuse comorbidities	Change in glucose tolerance Secondary Outcomes • Height, weight, and body fat percent change	January 2019
Laparoscopic Roux-en-Y Gastric Bypass Versus Laparoscopic Biliopancreatic Diversion	RCT	BPD/DS RYGB	N = 60 Age 20 – 50 Men and women BMI 50 – 60	BMI Metabolic normalization Gastrointestinal side-effects	April 2015

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
(BPD)- Duodenal Switch for Super obesity NCT00327912			No prior obesity surgery No severe disabling cardiopulmonary disease or malignancy		
The TRIABETES Study: A Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes NCT01047735	RCT	RYGB LAGB Lifestyle weight loss intervention	N = 60 Age 25 – 65 Men and Women BMI 30 – 35 with type 2 diabetes difficult to control with medication BMI 35 – 40 with type 2 diabetes No prior bariatric surgery No drug or alcohol addiction or cigarette smoking No poor overall health	Feasibility of RCT to compare two bariatric surgeries to lifestyle weight loss intervention Secondary Outcomes: Preliminary effectiveness information	April 2015

7. Methods

Objectives
The primary objectives of the systematic review were to:

1. Evaluate and compare the published evidence on the effectiveness of gastric bypass, gastric banding, sleeve gastrectomy, and biliopancreatic diversion (with or without duodenal switch) versus conventional weight-loss treatments in both adults and children/adolescents undergoing surgical treatment for obesity;

2. Evaluate and compare the published evidence on the effectiveness of gastric bypass, gastric banding, sleeve gastrectomy, and biliopancreatic diversion (with or without duodenal switch) when these procedures are compared directly in both adults and children/adolescents undergoing surgical treatment for obesity;

3. Evaluate and compare the published evidence on the harms of bariatric surgery procedures, including rates of procedure-specific and general surgical complications, longer-term morbidity, mortality, and requirements for procedure revision and/or reversal;

4. Identify the components of the management of patients undergoing bariatric surgery that appear to be correlated with "treatment success";

5. Determine the differential effectiveness and safety of the procedures of interest according to such patient and program/health-system factors as age, gender, race or ethnicity, comorbidities, BMI, smoking status, psychosocial health, surgeon experience, procedure volume, certification of the surgery center, and pre/post procedure support; and

6. Assess the costs and cost-effectiveness of the major bariatric procedures of interest in this analysis.

Analytic Framework
The analytic framework for this project is depicted on the following page. There were expected limitations on the available evidence in terms of (a) comprehensive comparisons of all four procedures, and (b) long-term data on effectiveness and potential harms. As such, judgments about the effectiveness of these interventions rested predominantly upon individual consideration of each type of surgery and its relevant comparators, evaluation of procedure-specific risks, and linkage of shorter-term outcomes to higher-quality data on long-term effects where available.

Figure 5: Analytic Framework for Bariatric Surgery
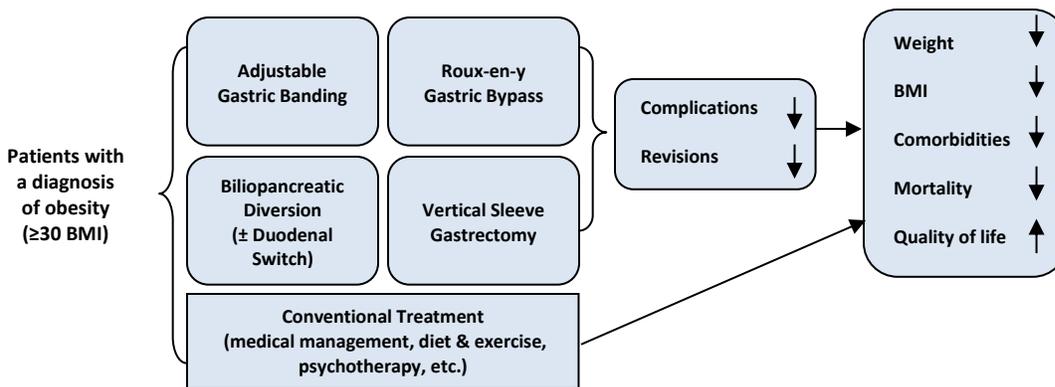
Patient Populations

The target population for this review included both adults and children undergoing surgical treatment for obesity; evidence from adult and pediatric studies was evaluated separately. All classifications of obesity (i.e., moderately, severely, and morbidly obese) within these categories were considered; among those who are moderately obese (i.e., BMI 30.0 – 34.9), studies were categorized according to major comorbidities present (e.g., type 2 diabetes, hypertension) when such descriptors were available.

Interventions

We evaluated the effectiveness of gastric bypass (RYGB), gastric banding (LAGB), sleeve gastrectomy (VSG), and biliopancreatic diversion (with or without duodenal switch) (BPD/DS). Studies that focused on the combination of bariatric surgery with pre- and post-operative psychotherapy and/or nutritional counseling were also included. We evaluated studies that compare these procedures to each other as well as those that compare bariatric procedures individually and collectively against conventional weight-loss treatments.

Finally, we have characterized detailed aspects of the intervention in each study, including components of pre-procedure preparation, level of post-procedure support, members of the treatment team, and definitions of treatment success or failure, where those definitions were available.

Comparators

The primary comparison of interest for this review was conventional weight-loss treatments. Those treatments deemed to be conventional include prescription medication, dietary supplements, diet-control programs, exercise, psychotherapy, and nutritional counseling. Conventional treatments may have been delivered individually or in combination. However, we restricted our assessment of comparisons of surgical to nonsurgical management to those studies involving some form of "active" conventional weight-loss management. We therefore excluded studies with wait-list comparators and "usual care" approaches if the approach was not described in any detail.

Outcomes

Outcomes of primary interest included rapid and sustained weight loss, changes in body weight/BMI, reduction of comorbidities (and associated medication use), improvements in health-related quality of life, and rates of complications, surgical revision and/or reversal, other longer-term procedure-related

morbidity (e.g., malabsorption), and mortality. Reduction of comorbidities included findings on improvement and/or resolution, as well as measures of positive and/or negative change in both physical (e.g., musculoskeletal pain) and psychiatric (e.g., depression, eating disorders) symptoms. Mortality was evaluated on both a peri-procedural (i.e., during the procedure or the 30 days following) and longer-term basis. Finally, given the interest in documenting specific components of the treatment approach in each study, we identified components correlated with higher levels of treatment success.

Information on the costs and cost-effectiveness of bariatric surgery procedures relative to each other and collectively compared to conventional treatment was summarized. We also developed a decision-analytic model evaluating the potential cost-effectiveness of these treatments in a setting germane to the Washington HCA. Although our model primarily focuses on the direct medical costs and short-term outcomes associated with the various treatment approaches (i.e., initial treatment, management of complications, re-treatment), we also included analyses that focus on the potential longer-term benefits, risks, and costs associated with each procedure.

Timeframe

Data on outcomes of interest were abstracted at all relevant timepoints. However, the focus of our assessment was on the perioperative benefits and risks of surgery (i.e., within 30 days) as well as the potential long-term effects. Because of this latter concern, we focused attention on longer-term comparative studies and/or timepoints in which at least 80% of the original sample was present (see "Study Quality" on page 29).

Study Designs

We included randomized controlled trials (RCTs) as well as comparative observational studies without restrictions on study design parameters. Observational studies of interest included those making explicit prospective or retrospective comparisons of each bariatric procedure of interest to another surgical method and/or to conventional weight-loss treatments.

Our primary focus of attention was on good- or fair-quality RCTs and comparative observational studies. However, for completeness, we abstracted data from case series with a minimum of two years of follow-up. Case series in adults were additionally limited to those with at least 100 patients; the sample size limit for children/adolescents was 25.

Data Synthesis

Data on relevant outcomes were synthesized quantitatively where feasible. Random-effects models were specified, and focused on odds ratios for binary measures such as comorbidity resolution. Weighted mean differences in continuous variables such as body weight/BMI and quality of life were also assessed. Qualitative evidence tables for the studies selected for review can be found in Appendix B.

Literature Search and Retrieval

The timeframe spanned the period from January 2000 to the most recently published data available. Evidence specifically in pediatric populations was considered an update to a review conducted for the Health Care Authority in 2007, which examined studies published through June 2007 (ECRI Institute, 2007). We focused on English-language reports only. Publications that appeared after the search period but prior to submittal of the final report were also be considered. The electronic databases we searched

as part of the systematic review included MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, PsycINFO, and CINAHL. Reference lists of all eligible studies were also searched and cross-referenced against public comments received by the HCA. 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 15,595 potentially relevant studies for this assessment (**Figure 6** below). After elimination of duplicate and non-relevant references, we identified 35 randomized control trials, 144 comparative cohort studies, and 96 case series, for a total of 275 included studies.

Figure 6: PRISMA flow chart showing results of literature search

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┌─────────────────────────┐
│ 15595 potentially        │
│ relevant references      │
│ screened                 │
└─────────────────────────┘
             │
             │              ┌─────────────────────────┐
             │              │ 12507 citations          │
             │              │ excluded                 │
             │─────────────▶│ Population: 54           │
             │              │ Intervention: 1123       │
             │              │ Comparator: 325          │
             │              │ Outcomes: 265            │
             ▼              │ Study Type: 5559         │
┌─────────────────────────┐│ Duplicates: 5181         │
│ 3088 references for full ││                          │
│ text review              │└─────────────────────────┘
└─────────────────────────┘
             │
             │              ┌─────────────────────────┐
             │              │ 2813 citations excluded  │
             │              │ (no surgical             │
             │              │ intervention, no         │
             │─────────────▶│ subgroup analysis for    │
             │              │ procedure type, no       │
             │              │ assessment prior to      │
             │              │ surgery, not a clinically-│
             ▼              │ relevant outcome)        │
┌─────────────────────────┐│                          │
│ 275 TOTAL                │└─────────────────────────┘
│ 35 RCTs                  │
│ 144 comparative cohorts  │
│ 96 case series           │
└─────────────────────────┘
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The most important outcomes for bariatric surgery are reduction in body weight/BMI, resolution of comorbidities, improvement in health-related quality of life, surgery-related complications, and mortality. Percentage of excess weight loss (%EWL) is a common metric used in studies of bariatric surgery to report weight loss that has been achieved relative to a defined goal (i.e., the patient's individualized ideal body weight); these data are reported where available. The harms of bariatric surgery include rates of procedure-specific and general surgical complications, longer-term morbidity, mortality, and requirements for procedure revision and/or reversal. Early complications are generally reported during the perioperative period up to 30 days after surgery, and complications are considered "late" if they occur beyond 30 days or persist for a period longer than this.

Study Quality

We used criteria published by the U.S. Preventive Services Task Force to assess the quality of randomized control trials (RCTs) and comparative cohort studies, using the categories "good," "fair," or "poor." Guidance for quality ratings using these criteria is presented below (AHRQ, 2008), as is a description of any modifications we made to these ratings specific to the purposes of this review. Note that case series are not considered as part of this rating system – because of the lack of comparator, these were universally considered to be of poor quality.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); 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, for RCTs, intention to treat analysis is used. Specifically for this review, target or mean/median duration of follow-up did not appreciably differ within study groups.*

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.*

8. Results

8.1 Overall Evidence Quality

While the comparative evidence base for either head-to-head comparisons of bariatric procedures or comparisons of bariatric surgery to nonsurgical interventions has grown considerably over time, major challenges with the quality and applicability of available studies remains. Of the 179 comparative studies identified for this evaluation, we rated only 26 (15%) to be of good quality, based on comparable groups at baseline, comparable duration of follow-up, and limited sample attrition. An additional 74 studies (41%) were rated fair quality; issues with comparability, duration of follow-up, and/or attrition were identified in these studies, but attempts were made to control for confounding in the analytic methods (e.g., survival analysis techniques, multivariate regression). However, we considered another 79 studies (44%) to be of poor quality because at least one key quality issue was present and not adequately addressed in either study design or analysis.

Specific quality issues with the evidence were as follows. Treatment groups were often imbalanced with respect to baseline characteristics with great potential to influence outcomes. For example, we considered any difference in mean pre-operative BMI greater than 3 increments to be potentially clinically significant. This was not only frequently encountered, but seldom controlled for in statistical analyses of outcome, even if that outcome was related to body weight or BMI. Many studies considered the within-subject change in BMI and other weight-related measures to be the most important outcomes of interest, and considered that justification for allowing some level of imbalance. No statistical differences were found in other studies even when large absolute differences were observed, but this appears to be a function of small sample size and consequent lack of statistical power to detect baseline differences.

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. Regarding the former, groups defined by surgical approach were often followed for different lengths of time because the procedures were performed by different groups or at different centers. In other cases, the difference in follow-up may have been planned—some studies focused on nutritional and/or metabolic outcomes after a certain threshold of weight loss, which frequently occurred over much longer period of time in nonsurgical control groups relative to surgical intervention (del Genio, 2007; Alam, 2011). In any case, no attempt was made in most studies to use appropriate statistical techniques to control for between-group differences in either baseline characteristics or duration of follow-up.

Attrition of the sample also appeared to be a common concern across studies, from small single-center evaluations to large registry studies. Even the widely-cited Swedish Obese Subjects (SOS) study, a matched prospective examination of bariatric surgery and nonsurgical management, saw a precipitous drop-off in patient availability after two years of follow-up (Sjöström, 2013; Sjöström, 2014). (Note: this study is not included in our primary analysis because over two-thirds of patients received gastroplasty, a procedure no longer performed in the U.S.; key findings from this study are nevertheless summarized in relevant sections to provide additional context.) Large-scale patient attrition is certainly understandable in these patients, given the clinical and mental complexity involved in obesity-related illness and the attendant difficulties for patients in adhering to post-procedure follow-up programs; however, very few studies accounted for patient attrition using well-accepted methods such as survival analysis and/or actuarial reporting. In all other studies, concerns with observing long-term results only in a small

percentage still adherent to the program are of critical importance, as the censoring is "informed"—those not receiving long-term benefits of bariatric surgery are more likely to be lost to follow-up.

Finally, most studies were lacking standardized definitions for important outcomes. For example, relatively few studies used an accepted classification system (e.g., Clavien) for categorizing the severity of procedure-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 type 2 diabetes was determined based on reductions of 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.

We identified 35 reports from 30 randomized controlled trials of bariatric surgery, four of which were rated to be of poor quality. Poor ratings for RCTs were a result of ineffectual randomization (e.g., BMI differences of >3 points, no control for these differences in analysis) and/or systematic differences in follow-up between groups (e.g., a surgical group studied for six weeks, a nonsurgical group evaluated over six months). Summary statistics for the good- and fair-quality RCTs are provided in **Table 2** on the following page, organized by type of comparison made. As shown in the table, not all studies reported on key outcomes of interest other than weight changes, such as resolution of comorbidities and procedure-related harms.

Of the remaining studies, 59 (34%) were prospective and 85 (59%) were retrospective cohort comparisons. Somewhat surprisingly, study quality was of essentially equivalent concern for both prospective and retrospective studies. A total of 29 of 59 (49%) prospective studies were rated poor quality, while 46 of 85 (54%) retrospective studies were rated poor. Reasons for a poor-quality rating were similar to those for RCTs—imbalanced treatment groups, differential follow-up and/or high patient attrition, and lack of use of statistical techniques to control for between-group differences.

Table 2: Available good- and fair-quality randomized controlled trials of bariatric surgery, by type of comparison:

Comparison	# Studies* / # patients	Range Of Follow-Up, Months (Median)	Measures (Studies Reporting)
Surgery vs. nonsurgical mgmt.	13 / 1,007	12-120 (24)	Weight (13) Comorbidity resolution (8) Harms (8)
RYGB vs. VSG	7 / 725	1-36 (12)	Weight (6) Comorbidity resolution (4) Harms (4)
RYGB vs. LAGB	2 / 248	50-120 (85)	Weight (2) Comorbidity resolution (1) Harms (2)
RYGB vs. BPD/DS	3 / 137	24-60 (48)	Weight (3) Comorbidity resolution (2) Harms (2)
Other surgical comparisons	1 / 80	36	Weight (1) Comorbidity resolution (0) Harms (1)

*31 reports of 26 distinct RCTs

RYGB: Roux-en-Y gastric bypass; VSG: vertical sleeve gastrectomy; LAGB: laparoscopic adjustable gastric banding; BPD/DS: biliopancreatic diversion with duodenal switch

> **Key Question #1a:** What is the comparative clinical effectiveness of bariatric surgery procedures versus conventional weight-loss management in adults (i.e., age 21 and older)?

Across a range of procedures, study designs, and duration of follow-up, bariatric surgery results in greater sustained weight loss and resolution of comorbidities (primarily type 2 diabetes) than nonsurgical interventions. These results are challenged by a lack of good-quality long-term data on durability of benefit. Long-term data that are available suggest that weight recidivism and comorbidity relapse are not uncommon, although more data are needed. Among types of bariatric procedures commonly performed in the U.S., biliopancreatic diversion with or without duodenal switch appears to produce the best outcomes, followed by gastric bypass, sleeve gastrectomy, and gastric banding. Evidence is insufficient to determine the comparative impact of any of these procedures or of nonsurgical care on long-term all-cause or cause-specific mortality.

The evidence comparing bariatric surgical procedures to conventional weight-loss management in adult patients is summarized below by key outcome of interest. For completeness, head-to-head comparisons of each type of bariatric procedure are also summarized as part of this key question. 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 noted major limitations 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). As noted previously, we did not include the SOS study in our analytic set because the primary surgical intervention was gastroplasty, which is no longer performed in the U.S. 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 large cohort 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), and 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 Veterans Affairs 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. However, a more recent VA-based evaluation examined all-cause mortality at multiple timepoints during 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 1-5 years, however, surgical patients experienced significantly lower rates of mortality (HR: 0.45; 95% CI: 0.36, 0.56); findings were similar at 5-14 years of follow-up.

Bariatric Surgery vs. Nonsurgical Management

We identified a total of 21 reports of good- or fair-quality RCTs (14) and prospective cohort studies (7) comparing one or multiple forms of bariatric surgery to nonsurgical management. Characteristics of included studies can be found in Appendix B. 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 type 2 diabetes (Courcolas, 2014; Dixon, 2008; Halperin, 2014; Ikramuddin, 2013; Leonetti, 2012; Liang, 2013; Mingrone, 2012; Schauer 2012, 2014; Scopinaro, 2011).

Impact of Bariatric Surgery 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 7 on the following 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 (I^2=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.

Noticeably missing from weight-change data is any analysis of long-term weight regain following surgery. The Swedish Obese Subjects (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 ten 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 U.S.). 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 kilograms 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.

Figure 7: Meta-analysis of mean BMI at study end: bariatric surgery vs. nonsurgical management
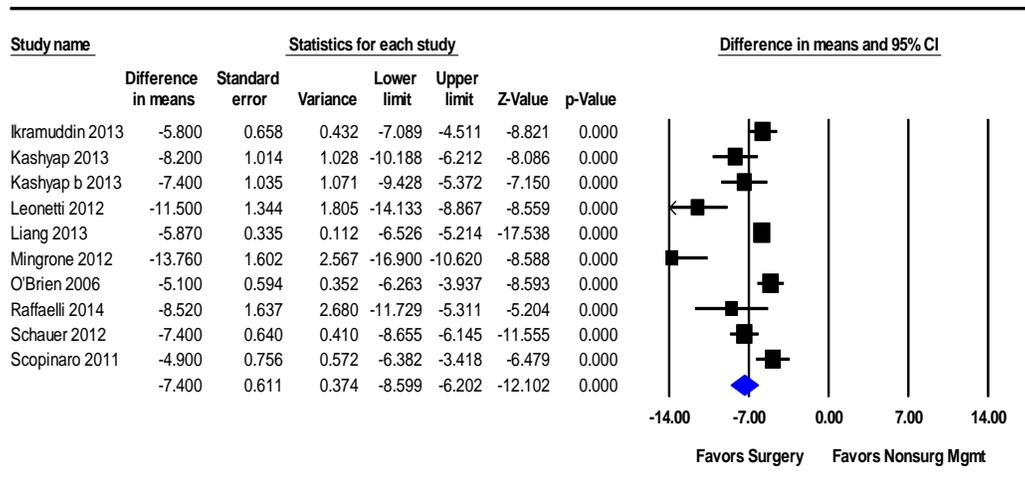
Study name	Statistics for each study							Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Ikramuddin 2013	-5.800	0.658	0.432	-7.089	-4.511	-8.821	0.000	
Kashyap 2013	-8.200	1.014	1.028	-10.188	-6.212	-8.086	0.000	
Kashyap b 2013	-7.400	1.035	1.071	-9.428	-5.372	-7.150	0.000	
Leonetti 2012	-11.500	1.344	1.805	-14.133	-8.867	-8.559	0.000	
Liang 2013	-5.870	0.335	0.112	-6.526	-5.214	-17.538	0.000	
Mingrone 2012	-13.760	1.602	2.567	-16.900	-10.620	-8.588	0.000	
O'Brien 2006	-5.100	0.594	0.352	-6.263	-3.937	-8.593	0.000	
Raffaelli 2014	-8.520	1.637	2.680	-11.729	-5.311	-5.204	0.000	
Schauer 2012	-7.400	0.640	0.410	-8.655	-6.145	-11.555	0.000	
Scopinaro 2011	-4.900	0.756	0.572	-6.382	-3.418	-6.479	0.000	
	-7.400	0.611	0.374	-8.599	-6.202	-12.102	0.000	

-14.00   -7.00   0.00   7.00   14.00

Favors Surgery   Favors Nonsurg Mgmt

Heterogeneity: Tau^2= 2.81; Q=55.8; df=9; I^2=84%

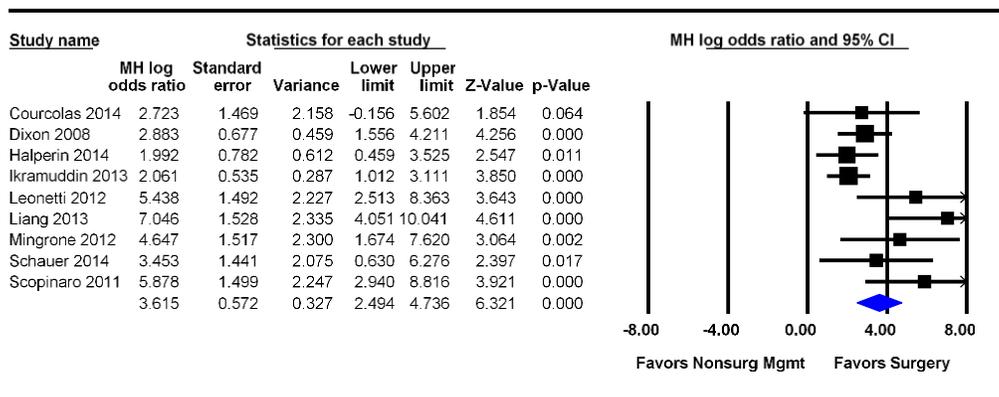Test for overall effect: Z=-12.1 (p<0.001)

Impact of Bariatric Surgery 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 type 2 diabetes. **Figure 8** the following page shows the results of our meta-analysis of resolution of type 2 diabetes 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 odds ratio [OR] 3.62; 95% CI 2.49, 4.74).

Although the results of the SOS study were not included in our meta-analysis, long-term data on diabetes remission are available. While 72% of surgery patients with type 2 diabetes 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 type 2 diabetes, however (96%, 84%, and 78% after two, 10, and 15 years, respectively) (Sjöström, 2012).

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 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 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%) vs. resolution in 7 of 15 (46.7%) (p<0.002 for the comparison). Similar patterns were observed in a ten-year follow-up from this study, although nearly half of those originally randomized to nonsurgical management crossed over to LAGB surgery (O'Brien, 2013).

Figure 8: Meta-analysis of resolution of type 2 diabetes: 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)

As with weight changes, degradation in performance of bariatric surgery with respect to comorbidity resolution was rarely evaluated in available RCTs. One RCT evaluated the performance of 150 patients with type 2 diabetes (mean age 48.5 years, 66% female, mean BMI 36) who were randomized to receive intensive medical therapy alone (lifestyle counseling, weight management, home glucose monitoring, and optimized use of antidiabetic medications), medical therapy + RYGB, or medical therapy + VSG and were followed for 12 months (Schauer, 2012). Achievement of HBA1c levels <6% was observed 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). Over 90% of the original sample was available for 3-year follow-up (Schauer, 2014); achievement of HbA1c <6% was reduced over this timeframe, but remained substantially higher in the surgical groups (38%, 24%, and 5% for RYGB, VSG, and medical therapy, respectively, p≤0.01 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).

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, defined as 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 type 2 diabetes 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 defined; 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.

Impact of Bariatric Surgery on Other Outcomes

Two studies reported the impact of bariatric surgery on health-related quality of life (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. In contrast, the 10-year follow-up of an RCT comparing LAGB to intensive medical therapy that was described on page 33 showed no statistically-significant differences between groups in the physical or mental summary component measures of the SF-36 (O'Brien, 2013).

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 type 2 diabetes (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 diabetes.
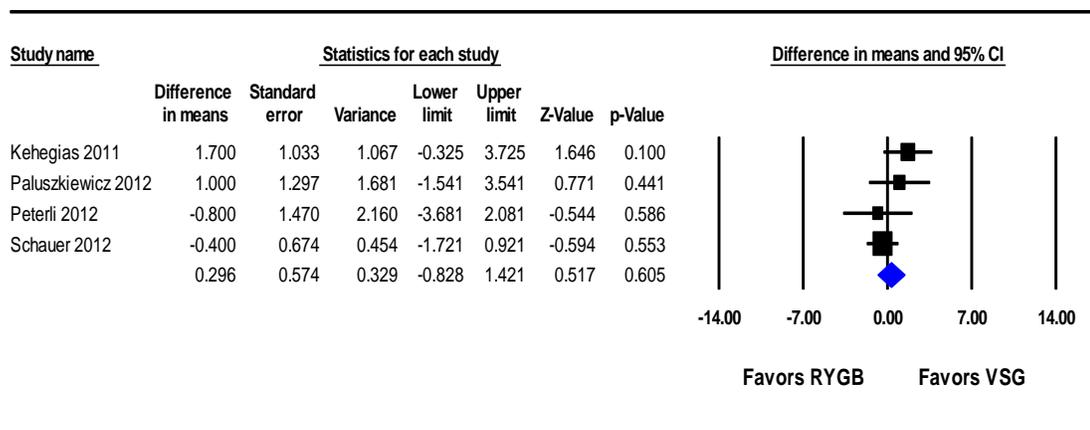
Gastric Bypass vs. Sleeve Gastrectomy

We identified a total of six RCTs and six prospective comparative cohort studies that met our criteria for good or fair quality, involved comparisons of RYGB to VSG, and had at least 12 months of follow-up. An additional RCT described previously compared both RYGB and VSG to nonsurgical management (Schauer, 2012). Characteristics of these studies and main results can be found in Appendix B.

Impact on Measures of Body Weight

Across all seven RCTs of interest (Kehagias, 2011; Paluszkiewics, 2012; Peterli, 2012; Peterli, 2013; Ramon, 2012; Schauer, 2012; Vix, 2013), reductions in BMI (11-15 points on average, irrespective of baseline values) and other measures of body weight change from baseline were substantial for both RYGB and VSG, but did not differ statistically in <u>any</u> of these studies. We conducted a meta-analysis of mean BMI at study end among those RCTs reporting these values along with appropriate measures of variance and drew similar conclusions (mean difference 0.30, 95% CI -0.83, 1.42) (see **Figure 9** below). Similarly, no statistical differences were observed in any of the prospective cohort studies. One cohort of 136 patients (mean age 42, 72% female, mean BMI 45) reported a percentage of excess BMI loss of 76% for RYGB at 2 years vs. 63% for VSG, but this difference was not tested statistically (Gehrer, 2010).

Figure 9: Meta-analysis of mean BMI at study end: RYGB vs. VSG

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Kehegias 2011	1.700	1.033	1.067	-0.325	3.725	1.646	0.100
Paluszkiewicz 2012	1.000	1.297	1.681	-1.541	3.541	0.771	0.441
Peterli 2012	-0.800	1.470	2.160	-3.681	2.081	-0.544	0.586
Schauer 2012	-0.400	0.674	0.454	-1.721	0.921	-0.594	0.553
	0.296	0.574	0.329	-0.828	1.421	0.517	0.605

Heterogeneity: Tau^2= 0.28; Q=3.7; df=3; I^2=20%

Test for overall effect: Z=0.52 (p=0.605)

Impact on Resolution of Comorbidities

Resolution of comorbidities was assessed as a binary variable in a total of four studies comparing RYGB to VSG (Benaiges, 2011; Benaiges, 2013; Paluzkiewicz, 2012; Peterli, 2013). Heterogeneity in study designs and patient populations precluded meta-analysis of these studies. As with body weight measures, comorbidity resolution was substantial for both types of surgery and did not statistically differ between groups for nearly all comparisons. In a cohort comparison of 140 patients (mean age 45, 82% female, mean BMI 46) who were followed for 12 months (Benaiges, 2011), resolution of hypertension did not differ between groups, but resolution of hyperlipidemia did (100% vs. 75% for RYGB and VSG respectively, p=0.014). An RCT of 217 patients (mean age 43, 72% female, mean BMI 44) (Peterli, 2013) found no statistical differences in one-year resolution of hypertension, dyslipidemia, diabetes, sleep apnea, back or joint pain, hyperuricemia (excess uric acid in blood), or depression between groups. A statistical difference was noted for resolution of gastroesophageal reflux disease (GERD), however (23% vs. 14% for RYGB vs. VSG, p=0.008).

Impact on Other Outcomes

Limited data were available from RCTs and prospective cohort studies on the comparative impact of RYGB vs. VSG on other key outcomes. In the Benaiges study of 140 patients (Benaiges, 2011), a 40-50% reduction in cardiovascular risk was observed using two scoring mechanisms with both procedures, but no significant differences were found between groups. In the previously-mentioned cohort study of 136 patients (Gehrer, 2010), a specific focus was placed on nutritional deficiencies following surgery. At a mean of two years of follow-up, significantly fewer patients undergoing VSG developed incident deficiencies in vitamin B_{12} (18% vs. 58% for RYGB, p<0.0001), and vitamin D (32% vs. 52%, p=0.02) as well as secondary hyperparathyroidism (14% vs. 33%, p=0.02).

Retrospective Cohort Studies

We identified 11 retrospective cohort studies of good- or fair-quality that compared outcomes for RYGB and VSG patients and had at least 12 months of follow-up (Carlin, 2013; Cutolo, 2012; Iannelli, 2013; Kruger, 2014; Lim, 2014; Nocca, 2011; Ortega, 2012; Skroubis, 2011; Vidal, 2013; Villarrassa, 2013; Zerrweck, 2014). No statistically-significant differences were found in any key measure of clinical benefit in nine of the 11 studies. One of these studies involved a matched comparison of nearly 9,000 patients receiving VSG, RYGB, or LAGB in a voluntary state registry in Michigan (mean age 46, 74% female, mean BMI 48) (Carlin, 2013). In the pairwise comparison of RYGB to VSG, the former was found to result in statistically-significantly greater excess weight loss, greater resolution of type 2 diabetes and dyslipidemia, and improved quality of life and patient satisfaction at three years versus VSG. The other study was a single-center evaluation of 77 "super-obese" (BMI 50-59.9 kg/m^2) patients who were followed for one year (Zerrweck, 2014). The percentage of excess weight lost at one year was significantly higher in the RYGB group (64% vs. 44% for VSG, p<0.05).

Gastric Bypass vs. Gastric Banding

We identified three RCT reports and four prospective comparative cohort studies of good- or fair-quality that evaluated outcomes for RYGB and LAGB over a minimum of 12 months of follow-up. Details of each study and main results can be found in Appendix B. Of note, two of the RCT reports related to five- and 10-year follow-up from a single RCT (Angrisani 2007; Angrisani 2013). Differences in study design and the outcomes measured precluded formal meta-analysis of outcomes in this comparison set; study findings are nonetheless summarized descriptively below.

Impact on Measures of Body Weight

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 excess weight loss 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). Excess weight loss remained in favor of RYGB (69% vs. 46% for LAGB, p=0.03).

The other RCT was a fair-quality evaluation of 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. Excess weight loss 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% excess weight loss, occurred in 17% of LAGB patients and zero RYGB patients (not statistically tested).

Similar findings were observed in the five prospective cohort comparisons (Bowne, 2006; Cottam, 2006; Puzziferri, 2008; Weber, 2004). The largest of these examined 1,733 individuals (1,102 and 631 for RYGB and LAGB respectively) (mean age 44, 85% female, mean BMI 50) at a single large institution, and followed patients for two years (Puzziferri, 2008). Excess weight loss was statistically-significantly greater for RYGB at two years (75% vs. 44% for LAGB, p<0.0001), and RYGB patients achieved >40% excess weight loss more quickly than their LAGB counterparts.

Impact on Resolution of Comorbidities

Resolution of comorbidities was assessed in binary fashion in one of the RCTs and three cohort studies. Five-year data from the Angrisani RCT (Angrisani, 2007) indicated that diabetes, hyperlipidemia, and sleep apnea had resolved in the four patients with these conditions at baseline, regardless of surgical assignment. The only measured comorbidity that remained unresolved was hypertension in three LAGB patients at baseline.

Results were somewhat mixed in the cohort studies. In an evaluation of 106 individuals (mean age 43, 80% female, mean BMI 56) followed for a median of 16 months (Bowne, 2006), RYGB was associated with significantly greater resolution of sleep apnea (88% vs. 39%, p=0.01), but no statistical differences in resolution of diabetes, hypertension, dyslipidemia, asthma, or arthritis. In contrast, a matched evaluation of 362 patients (mean age 43, 84% female, mean BMI 47) followed for up to three years found statistically greater levels of resolution of diabetes, hyperlipidemia, and hypertension among those receiving RYGB (Cottam, 2006). Finally, another matched comparison of 206 patients (mean age 40, 79% female, mean BMI 48) showed statistically greater resolution of type 2 diabetes and dyslipidemia among RYGB patients, but no statistical difference in hypertension.

Impact on Other Outcomes

Limited data were available on the comparative impact of RYGB vs. LAGB with regard to other outcomes. The previously-mentioned Bowne cohort study of 106 patients (Bowne, 2006) measured patient satisfaction using a 4-point rating system, and found that 80% of RYGB patients reported that

they were very satisfied with the procedure vs. 45% receiving LAGB (p=0.006). The Nguyen RCT evaluated the impact of surgery on health-related quality of life using the SF-36 (Nguyen, 2009); while some differences in certain domains were noted at earlier timepoints, no statistically-significant differences were noted in individual domains or summary scores by 12 months of follow-up.

Retrospective Cohort Studies

Comparisons of RYGB to LAGB were performed in 13 retrospective cohort studies following patients for at least one year (Arterburn, 2014; Campos, 2011; Carlin, 2013; Galvani, 2006; Jan, 2007; Kim, 2006; Kruger, 2014; Mueller, 2008; Parikh, 2005, 2006; Pohle-Krauza, 2011; Romy, 2012; te Riele, 2008; Zuegel, 2012). Details of these studies can be found in Appendix B. Findings mirrored those of available RCTs and prospective cohort studies in all but one of these retrospective evaluations. In an evaluation of 590 patients treated at a single center (mean age 41, 80% female, mean BMI 47), differences in excess weight loss at 12 months were similar to that reported in other studies (65% vs. 39%, p<0.001) (Galvani, 2006). By 18 months, however, differences had narrowed (63% vs. 55%) and were no longer statistically significant. No data were provided on attrition of the study sample from 12 to 18 months.

Gastric Bypass vs. Biliopancreatic Diversion (With or Without Duodenal Switch)

We identified five reports on three RCTs (Hedberg, 2012; Olsen, 2012; Risstad, 2015; Søvik, 2010 and 2011) and one prospective cohort study (Nanni, 2012) directly comparing RYGB with BPD, with or without DS, of good- or fair-quality, and with follow-up of at least 12 months. Details of each study and major findings are provided in Appendix B.

Impact on Measures of Body Weight

In the three available RCTs, there was consistent and statistically-significantly greater reductions in measures of body weight with BPD/DS relative to RYGB, with mean reductions of 6-8.5 BMI points in all three studies. Unfortunately, appropriate measures of variance were available in only two of these RCTs, so meta-analyses were not conducted. Findings were similar for the prospective cohort study (Nanni, 2012), but could not be included in a meta-analysis because of a lack of hypothesis testing of body-weight measures.

The durability of procedure performance was examined in the three reports of the Søvik RCT. In the 2010 Søvik study, 60 super-obese patients (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). Significant differences in body weight and excess BMI lost were noted in both reports. 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).

Impact on Resolution of Comorbidities

Information on resolution of comorbidities in this comparison set was extremely limited. In an RCT of 47 super-obese patients (mean age 39, 47% female, mean BMI 54) who were followed for up to four years (Hedberg, 2012), the percentage of patients achieving an HbA1c level <5% was reported to be 100% in the BPD/DS group vs. 82% in the RYGB group, although this was not statistically tested. In another small RCT of 30 super-obese patients (mean age 35, 67% female, mean BMI 55) who were followed for two years (Olsen, 2012), the presence of sleep apnea was self-reported by one patient in the BPD/DS group,

but this was not tested statistically, nor was it compared to baseline prevalence. Long-term follow-up of the Søvik study in the super-obese (see above) yielded no statistically-significant differences in remission of type 2 diabetes or metabolic syndrome (Risstad, 2015).

Impact on Other Outcomes

Limited data were available from RCTs and prospective cohort studies on the comparative impact of RYGB versus BPD/DS on other outcomes. A single report of an RCT (Risstad, 2015) included outcomes on health-related quality of life and nutritional deficiencies after five years of follow-up.   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 surgery groups. The rate of newly-diagnosed nutritional deficiencies also did not statistically differ.

Retrospective Cohort Studies

We identified five retrospective cohort studies that met our quality criteria and followed patients for at least 12 months (Deveney, 2012; Nelson, 2012a; Parikh, 2006; Prachand, 2006; Skroubis, 2011). Findings with respect to weight-loss measures were similar to those seen in the prospective evaluations. One evaluation provided more detailed information on comorbidity resolution than presented in prospective studies. This was an analysis of data from a large multicenter registry database, comparing 1,545 BPD/DS patients with a control group of 77,406 undergoing RYGB (Nelson, 2012a). Demographics were similar between the two groups (mean age 45, 78% female), but mean BMI was significantly higher in the BPD/DS group (52 vs. 48, p<0.001). Nonetheless, the pre-operative prevalence of hypertension and dyslipidemia was similar in the two groups, and these were resolved to a significantly greater extent by BPD/DS (58% vs. 47% for hypertension and 68% vs. 44% for dyslipidemia, p<0.001 for both comparisons).

Other Surgical Comparisons

Data were limited for other surgical comparisons. We identified a single RCT and single prospective cohort study that met quality and follow-up criteria and involved comparisons other than those described above (Brunault, 2011; Himpens, 2006). Both were comparisons of LAGB to VSG. In the RCT, 80 patients (mean age 38, 80% female, mean BMI 38) were randomized to LAGB or VSG and followed for three years (Himpens, 2006). VSG was associated with a statistically-significantly greater percentage of excess weight lost (66% vs. 48% for LAGB, p=0.0025), as well as statistically-significantly greater changes in BMI (median of -27.5 vs. -18, p=0.0004) and body weight (-29.5 vs. -17, p<0.0001). Findings were less dramatic after one year of follow-up in a prospective cohort of 131 patients (mean age 40, 82% female, mean BMI 50) (Brunault, 2011), but still favored VSG for excess weight loss (44% vs. 35%, p=0.02) as well as significant improvement on the psychosocial domain of the Quality of Life, Obesity, and Dietetics (QOLOD) rating scale.

Surgical comparisons were varied and heterogeneous in retrospective cohort comparisons. They are therefore not summarized here but are available for review in Appendix B.

Key Question #1b: What is the comparative clinical effectiveness of bariatric surgery procedures versus conventional weight-loss management in children (age <21), on an overall basis and by specific age groups (i.e., 18-20, 13-17, 12 or less)?

There is a lack of both short- and long-term data demonstrating effectiveness for any bariatric surgery procedure in both children and adolescents. We found only two studies of sufficient quality: one RCT (O'Brien, 2010) which compared LAGB to conventional weight-loss treatment, and one retrospective cohort (Messiah, 2013) comparing LAGB to RYGB. Six additional comparative cohorts were identified but these studies were determined to be of poor quality; one of these studies is described in detail below because of its large sample size (see Appendix B for information on additional poor quality studies). Only one case series (Silberhumer, 2011) evaluating the long-term effects of LAGB in adolescents met our criteria for inclusion. There were no comparative studies evaluating any bariatric procedure exclusively in children (under 13 years) or the use of BPD in any patient under 21 years old.

We identified a single 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 29.6kg/m² in the surgical cohort and 39.2kg/m² in the lifestyle intervention group, representing a significantly greater percentage of excess weight loss 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.

Despite being of generally good quality, this study has some important limitations. First, although the authors used recruitment measures to minimize bias to treatment, these results may reflect the subset of patients who had access to surgical intervention without barriers to insurance coverage. In addition, while the study was powered to report on changes in weight, the authors were limited by the small sample size in assessing statistical differences between groups for other health-related outcomes, including adverse events. Finally, because of the relatively short duration of the study (2 years), the authors could not comment on the long-term benefits of surgery.

Of the five comparative cohort studies we identified in our literature 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 timepoint, patients in both groups had significant weight loss and significant improvement of comorbidities, including diabetes, 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.

There are some methodological concerns with this study beyond its retrospective design. As with other comparative studies on bariatric surgery, long-term safety and efficacy data are absent. The authors note that the data entry into BOLD is performed by participating surgeons and may underrepresent true rates of complications. There is also a concern with missing follow-up data for all bariatric outcomes – an issue that is even more prevalent in an older adolescent population who are more mobile than in adults – which may have introduced selection bias. Nevertheless, the authors tested for potential differences between groups with and without complete follow-up data and found no differences.

Of the six poor-quality comparative cohorts, one retrospective study (Lennerz, 2014) involved 345 patients (mean age 19, 67% female, mean BMI 47.4) between 8-21 years who received either RYGB, LAGB, or VSG over one and a half years of follow-up. Patients in the RYGB group had the largest reduction in BMI compared to either VSG or LAGB (-32.9%, -29.4%, -20.0% for RYGB, VSG, and LAGB, respectively, p<0.001), and there were no statistical differences for weight loss outcomes between patients <18 and 18-21 years old. Prevalence of comorbidities also decreased, including diabetes, hypertension and sleep apnea; these data are not reported by procedure, however. Although this was the largest of the poor-quality comparative studies, there are serious quality concerns, including unmatched groups at baseline and a high attrition rate with only 48% of the original population available for follow-up.

In order to assess long-term outcomes of bariatric surgery in an adolescent population, we also 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 our criteria for inclusion. 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 5 years, with only 10% lost to follow-up, the mean BMI was 27.3 kg/m², representing a mean excess weight loss of 92.6%, and the difference between timepoints was significant up to 3 years (p<0.01). All patients with a functional band had 100% resolution of all comorbidities, and quality of life after surgery continued to improve over time with significant differences between all points of follow-up up to five years (p=0.01).

We identified four additional case series with 217 patients that met our inclusion criteria for sample size and mean duration of follow-up – three evaluating the use of VSG and one evaluating LAGB – for a total of 267 patients across all studies. However, none of these studies maintained at least 80% enrollment throughout follow-up duration. Mean age ranged from 15.8 to 19.5 years old, and excess weight loss ranged from 61.1% to 101.6%. Mortality was either not reported or no deaths occurred. Details on all the case series relevant to our analysis are represented in **Table 3** on the following page.

Table 3: Case series with >2 years of follow-up in children/adolescents undergoing bariatric surgery

Study	Boza 2012	Nadler 2008	Nocca 2014	Raziel 2014	Silberhumer 2011
Procedure	VSG	LAGB	VSG	VSG	LAGB
# patients @ baseline	51	73	61	32	50
Mean age/BMI	18.0/38.5	15.8/48	19.5/45.7	16.8/43.2	17.1/45.2
%EWL @ study end	92.9	61.0	78.4	101.6	92.6
Mean f/u	2 years	2 years	2 years	60 months	86 months
Max point with 80% f/u	1 year	<6 months	6 months	3 months	5 years
# patients with 80% f/u	34	16	5	2	45
Reoperations	1	11	1	2	6

BPD = Biliopancreatic Diversion; LAGB = Laparoscopic Adjustable Gastric Banding; RYGB = Roux-en-Y Gastric Bypass; VSG = Vertical Sleeve Gastrectomy; %EWL = percentage of Excess Weight Loss; f/u = follow-up, BMI = Body Mass Index

In order to understand whether our selection criteria eliminated valuable case series data in certain subgroups of pediatric patients, we evaluated data from a recently published systematic review that used less restrictive criteria (i.e., 10 or more patients, no restrictions on follow-up) (Black, 2013). Even with these relaxed criteria, a total of only 637 patients were evaluated across 23 included studies, only two of which allowed children under 12. A meta-analysis of change in BMI from baseline in these studies suggested a substantial reduction (weighted mean difference: -13.5; 95% CI: -15.1, -11.9), but when stratified by procedure, data were only considered sufficiently robust for RYGB (results were highly variable with LAGB, and there were too few studies of VSG or BPD/DS). Data on resolution of comorbidities and complications were not included in all studies, and reporting methods were not consistent enough to allow for meta-analysis of these data.

Key Question #2: What components of the management of patients undergoing bariatric surgery (e.g., selection of candidates for surgery, multi-disciplinary care team, pre- and/or post-procedure counseling and support) appear to be correlated with higher levels of "treatment success" (e.g., sustained weight loss, reduction in comorbidity burden, etc.)?

Several patient characteristics and programmatic factors have been associated with higher levels of treatment success. Younger patients and those with lower pre-operative BMIs achieve greater excess weight loss after surgery. There is not a consistent correlation between comorbidity status and weight loss, although type 2 diabetes status has been found to have an inverse relationship with weight loss. Multi-disciplinary care, consistent follow-up, and post-operative counseling appear to be essential to producing better outcomes. Patient motivation is also an important factor in achieving successful weight loss. Low surgeon or hospital volume is associated with greater mortality and complications, as are older age and male gender.

Several components of the management of patients undergoing bariatric surgery have been found to be correlated with higher levels of treatment success. Both programmatic factors and certain candidate characteristics have been attributed with a higher likelihood of greater and sustained weight loss. Programmatic factors are discussed more extensively in Key Question 4. The key factors of each of the studies reviewed for this question are summarized in Appendix C.

Selection of Candidates

Certain patient characteristics make eligible candidates more or less likely to have success in bariatric surgery. As discussed in further detail in Key Question 5, studies have had inconsistent findings in relation to gender and weight loss: depending on the statistic reported (i.e., BMI change, kilograms lost, excess weight loss [EWL]), some studies report EWL to be greater in females (Melton, 2008; Bueter, 2007; Dallal, 2009; Chen, 2012; Carlin, 2013), greater in males (Dallal, 2009; Compher, 2012; Messiah, 2013; Ma, 2006; Sarwer, 2008), or without statistical differences (Lutfi, 2006; Ortega, 2012; Perugini, 2003).

Age and baseline BMI have been consistently reported to be negatively associated with EWL, with heavier and older patients losing a lower percentage of weight (Ortega, 2012; Carlin, 2013; Chevallier, 2007; Ma, 2006; Still, 2014). For example, a matched cohort study of 8,847 patients (mean age 46, 74% female, mean BMI 48 kg/m^2) found that EWL was 5.7%, 8.1%, and 13.5% lower for patients 60 years of age or older after 12 months follow-up, compared to patients under 30 years of age for RYGB, VSG, and LAGB, respectively (Carlin, 2013).

A number of studies have shown an inverse correlation between diabetes status and weight loss success: having type 2 diabetes is associated with less weight loss after surgery (Melton, 2008; Wittgrove, 2000; Ma, 2006; Perugini, 2003; Ortega, 2012; Still, 2014). In an analysis of weight data from 555 RYGB patients, Melton et al. reported that type 2 diabetes patients had an odds of suboptimal weight loss, which they defined as <40% EWL, of 2.6 (95% CI: 1.5, 4.8) (Melton, 2008). Other comorbidities such as depression and binge eating disorder have <u>not</u> shown a correlation with weight loss (Ma, 2006).

Whereas weight loss outcomes have been inconsistent in relation to gender, mortality and complication findings have not: several studies have found male gender to be associated with greater mortality,

longer length of hospital stay, and higher rates of complications (Masoomi, 2011; Nguyen GC, 2013; Nguyen, 2011; Padwal, 2013).

Several other patient characteristics are associated with greater mortality, including race, and older age (Masoomi, 2011; Nguyen, 2013; Nguyen, 2011; Padwal, 2013). Comorbidity status at baseline is associated with greater complication rates (Masoomi, 2011; Perugini, 2003; Padwal, 2013; Ortega, 2012) although evidence of mortality in relation to obesity-related comorbidities such as hypertension and type 2 diabetes has been inconsistent.

Psychiatric comorbidity also may adversely affect patient selection. Although adequate perioperative counselling is suggested to improve the results of surgery, patients with social phobia and avoidant personality disorders are less willing to participate (Lier, 2011). In a study of 363 patients eligible for RYGB or VSG, Sockalingam et al. (2013) showed that eligible bariatric surgery candidates who did not follow through with surgery had significantly higher rates of overall past Axis I psychiatric disorders than patients who completed surgery (58.1 vs. 46.6 %, p=0.035), past anxiety disorders (17.4 vs. 9.4 %, p=0.03), and past substance use disorders (8.7 vs. 3.7 %, p=0.03).

Programmatic Factors

In addition to age, baseline BMI, and diabetes status, a few key programmatic factors have been associated with surgical success. First, a multidisciplinary care approach has become a common element of bariatric surgery, both before and after the procedure. We found only 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/m2) 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 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.

Not surprisingly, program adherence after surgery has 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 calculated that the odds of $\geq$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). Correspondingly, adherence to scheduled follow-up visits and compliance with recommended post-operative care, predict a greater decrease in BMI during the first 4 years after LAGB[2] (Pontiroli, 2007).

As discussed in further detail in Key Question 4, participation in post-operative support groups has been associated with better weight outcomes (Nijamkin, 2012; Nijamkin, 2013, Elakkary, 2006). However it is uncertain whether dietary counseling following surgery improves outcomes. While there have been

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

many studies assessing the effectiveness of _pre-operative_ dietary counselling and weight loss programs (Carlin, 2008; Harnisch, 2008; Huerta, 2008; Jamal, 2006; Becouarn, 2010; Van Nieuwenhove, 2011; Parikh, 2012; Alami, 2007), we found only one study that analyzed post-operative dietary counseling (Sarwer, 2012). In this study, 84 patients (mean age 42, 63% female, mean BMI 52 kg/m2) undergoing RYGB or LAGB were randomized to receive either dietary counseling or standard postoperative care for the first four months after surgery (Sarwer, 2012). The participants completed measures of macronutrient intake and eating behavior at baseline and 2, 4, 6, 12, 18, and 24 months after surgery.While the patients who received dietary counseling achieved greater numeric weight loss than those who received standard care, the difference did not reach statistical significance. Similarly, while dietary counseling patients consumed fewer calories (1,170 vs. 1,463), more protein (10% of daily intake vs. 13%) and less sweets (46% of daily intake vs. 50%) than patients who were not counseled, these differences did not reach statistical significance (Sarwer, 2012).

Psychosocial Factors

Certain psychosocial factors may also impact levels of surgical success. Weineland and colleagues randomized 39 bariatric patients who underwent either sleeve gastrectomy or gastric bypass surgery (mean age 43, 90% female, mean BMI 37 kg/m2) to two post-operative approaches: (1) acceptance and commitment therapy (ACT), including two face-to-face sessions and support via an Internet application; or (2) treatment as usual (TAU) comprising the standard follow-up used by the surgical team. Participants in the ACT condition significantly improved on subjective binge eating (F(1,37)=8.38, p=0.006, effect size η^2_p=0.19), body dissatisfaction (F(1,37)=5.65, p=0.023, effect size η^2_p=0.13), quality of life (F(1,37)=7.65, p=0.022, effect size η^2_p=0.13) and acceptance of weight related thoughts and feelings (F(1,37)=8.59, p=0.006, effect size η^2_p=0.18), as compared to those in the TAU group (Weineland, 2012).

Support groups and counseling can help patients modify their lifestyles, adhere to care guidelines, and have better overall outcomes. Those who participate in post-operative support groups have had better weight loss outcomes than those who do not (Orth, 2008a; Weineland, 2012). Orth et al. (2008a), for example, found that RYGB patients who attend support groups have a significantly greater decrease in BMI than patients who do not attend such groups (42% vs. 32%; p<0.03).

With the exception of pre-surgical weight loss requirements (discussed in further detail in Key Question 4), few studies have analyzed pre-operative interventions. We found two studies that looked at pre-surgical counseling (Lier, 2012; Leahey, 2009). Interestingly, these studies found that patients had poorer attendance at pre-operative counseling sessions and did not have significantly different weight loss from patients who did not participate in any sessions. For example, in an RCT of 141 patients (mean age 42, 73% female, mean BMI 45.2 kg/m2) undergoing gastric bypass surgery, patients were randomized to receive psychological group counseling before surgery or "treatment as usual" (Lier, 2012). After one year of follow-up, the groups showed no statistical differences regarding weight loss or adherence to lifestyle changes in diet and physical activity. Another prospective study compared 32 pre-operative and post-operative LAGB and RYGB patients (mean age 49, 78% female, mean BMI 44 kg/m2) who had been referred to a 10-week intervention designed to reduce eating behaviors associated with postoperative weight gain (e.g., loss of control while eating, grazing) (Leahey, 2009). Compared to post-surgical patients, pre-surgical patients attended fewer sessions (t(18)=2.51, p=0.02) and were less likely to complete the intervention (14% pre-surgical completers vs. 91% post-surgical completers, p=0.007) (Leahey, 2009).

Self-selecting to attend meetings or adhere to care recommendations may be the result of other intrinsic patient characteristics, such as discipline or motivation, which make patients more likely to have weight loss success and adhere to post-operative care recommendations (Ray, 2003). In an analysis of data from 149 RYGB patients (mean age 29, 81% female, mean BMI 52 kg/m2) operated on by the same surgeon, Ray and colleagues found that patients who perceived "moderate to severe obesity-related health problems" in themselves lost a greater percentage of excess weight loss than those who did not perceive such problems in themselves (59% vs. 43%, p<0.05). Moreover, those who reported that their motivation for seeking weight loss surgery was not from an extrinsic pressure (such as social distress from obesity) but rather an intrinsic drive to lose weight, were also more successful (62% vs. 53%, p<0.05) (Ray, 2003).

In addition to predicting weight loss success, several studies have analyzed factors predictive of mortality and complications. As discussed in more detail in Key Question 4, hospitals and surgeons with lower case volume tend to have higher rates of complications and mortality (Birkmeyer, 2010; Gould, 2011; Courcoulas, 2003; Nguyen, 2004; Murr, 2007; Perugini, 2003; Smith, 2013; Weller, 2007). Murr et al. (2007) used a multiple variable binary logistic regression model adjusting for patient age, gender, and procedure calendar year and found a significant association between a surgeon's procedure volume and the odds of developing an in-hospital complication: patients who underwent a procedure from a surgeon who had performed 1-5 procedures in the five years of the study (relative to a patient whose surgeon had undertaken ≥500 procedures) had an odds of developing a complication of 2.0 (95% CI: 1.3, 3.1). (Murr, 2007). Similarly, Nguyen and colleagues report a similar relationship between mortality and hospital volume: compared to centers that performed less than 50 procedures a year, the odds of mortality were one third less among centers that performed 100-199 procedures (OR 0.65; 95% CI: 0.21, 0.45) (Nguyen, 2013).

Key Question #3: What are the potential short- and long-term harms of bariatric surgery procedures, including rates of procedure-specific and general surgical complications, longer-term morbidity, mortality, and requirements for procedure revision and/or reversal?

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 Table 4. 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 has the complication rate (31.6%). Most studies were small and underpowered to detect any statistical differences between procedures for adverse events, 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 cohorts 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 4 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 data for each study can be found in Appendix D; in addition, findings are reported in detail for each surgical comparison in the sections that follow.

Table 4: 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

BPD = Biliopancreatic Diversion, LAGB = Laparoscopic Adjustable Gastric Banding, RYGB = Roux-en-Y Gastric Bypass, VSG = Vertical Sleeve Gastrectomy

*Complication rate may include reoperations in some studies.

Randomized Controlled Trials

Gastric Bypass vs. Sleeve Gastrectomy

We found only one good quality RCT (Schauer, 2012) that compared RYGB to VSG and included data on harms. This study evaluated 150 patients (mean age 49, 66% female, mean BMI 37) assigned to RYGB, VSG, or conventional weight-loss treatment and found that VSG had fewer reoperations (1 vs. 3) and fewer adverse events requiring hospitalization (4 vs. 11) than RYGB, but the study was underpowered to detect statistical differences between groups. No patients died, and there were no life-threatening complications for any study participant. During the three-year follow to this study (Schauer, 2014), with 91% patients remaining, additional minor complications occurred in both groups, (5 vs. 3 for RYGB and VSG, respectively) but there were no major late complications, reoperations, or deaths.

Three fair quality RCTs (Paluszkiewics, 2012; Kehagias, 2011; Peterli, 2013) also compared RYGB to VSG up to 3 years of follow-up, and all concluded that the procedures had similar outcomes with regards to safety. The first study (Paluszkiewics, 2012) evaluated 72 patients (mean age 44, 86% female, mean BMI 47.4) over one year and found no significant differences for early (6 vs. 7 for VSG) or late (22 in each group) complications, or reoperations (1 vs. 0 for VSG). Another RCT (Peterli, 2013), which followed 217 patients (mean age 43, 72% female, mean BMI 43.9) for a mean of two years, found that while more patients in the RYGB group required reoperation (5 vs. 1 for VSG) and greater frequency of perioperative morbidity (19 vs. 9 for VSG), these differences were not statistically significant. The final RCT (Kehagias, 2011) included 60 patients (mean age 35, 60% female, mean BMI 45.4) with the longest duration of follow-up (3 years) found that early morbidity was more common in the VSG group (13 vs. 10 for RYGB), though this difference was not statistically significant. In addition, while significantly more patients experienced vitamin B12 deficiency after RYGB (7 vs. 1 patient for VSG, $p<0.05$), reoperations and late morbidity occurred with the same frequency in both groups. There was one death related to surgery among all 176 patients in the RYGB group, which was the result of gastrojejunostomy leakage.

Gastric Bypass vs. Gastric Banding

There were two good-quality RCTs (Angrisiani, 2007 and Angrisiani, 2013; Courcoulas 2014) comparing RYGB to LAGB. One of these studies (Angrisani, 2007) evaluated 51 patients (mean age 34, 82% female) mean BMI 43.6) undergoing LAGB or RYGB over a five-year period. During the perioperative period, two patients in the RYGB group had reoperations – one patient had a conversion to laparotomy and another had a jejunal perforation requiring surgical intervention. No patients in the LAGB cohort had any complication requiring an additional procedure, but it is not clear if other minor complications occurred. After 30 days, two LAGB patients required a reversal surgery and one RYGB patient had a small bowel obstruction requiring another surgery. In the 10-year follow-up to this RCT (Angrisani, 2013), an additional seven operation occurred in the LAGB group, all of which were the result of band removal, while three occurred in the RYGB group, bringing the total number of overall complications to nine in the LAGB group and eight in the RYGB group. Study retention was more than 80% for both cohorts, and no patient died. Another RCT (Courcoulas, 2014) of good quality followed 69 patients (mean age 47, 81% female, mean BMI 35.5) for one year and found that more LAGB patients experienced an adverse event (3 vs. 1 for RYGB), including one reoperation to replace a detached port. No patient died in any study.

Conversely, a fair quality RCT (Nguyen, 2009) of 197 patients (mean age of 44, 77% female, mean BMI 47) found that subjects in the RYGB cohort experienced significantly more complications than those undergoing LAGB (50 vs. 15 patients, p<0.01). Nearly half of the complications in the RYGB cohort occurred in the perioperative period, seven of which were major complications including postoperative bowel obstruction in five patients and postoperative gastrointestinal hemorrhage in two patients. Only two major complications, including one gastrointestinal hemorrhage and an internal herniation, occurred in the LAGB group during the same time period. Although late complications were also more frequent in the RYGB group (43 vs. 10 for LAGB), fewer patients had a reoperation, though this difference was not statistically significant (8 vs. 10 for LAGB). The mean follow-up for the LAGB cohort was shorter (3.6 vs. 4.2 years) and had fewer subjects available for assessment (80 vs. 92 patients) than the RYBG group, so late complications and reoperations may be underreported. There were no deaths over the entire study period.

Gastric Bypass vs. Biliopancreatic Diversion (With or Without Duodenal Switch)
We identified five reports of three RCTs (Hedberg, 2012; Mingrone, 2012; Risstad, 2015; Søvik, 2010 and Søvik, 2011) comparing the differences between RYGB and BPD, all of which were of good quality. However, no study had more than 60 patients and only one RCT (Søvik, 2010; Søvik, 2011, Risstad, 2015) was powered to detect statistical differences. In this study, which evaluated 60 patients (mean age 36, 70% female, mean BMI 55) over one year, no differences were found for early (4 vs. 7 for BPD) or late complications (5 vs. 9 for BPD), or reoperations (2 vs. 1 for BPD), though the RYBG group had fewer occurrences throughout the study period. After an additional year of follow-up (Søvik, 2011), there were an additional 10 complications and six reoperations for RYGB, and an additional six complications and one reoperation in the BPD group. For the RYGB patients, most of these late complications included cholelithiasis and abdominal pain, while patients in the BPD group experienced more frequent occurrences of vomiting and malnutrition. After five years of follow-up, the overall complication rate was comparable between groups, but BPD/DS was associated with a significantly higher rate of hospital admission (59% vs. 29%, p=0.02) and complications requiring surgical intervention (45% vs. 10%, p=0.002) (Risstad, 2015).

In the Hedberg study (Hedberg, 2012), which followed 47 patients (mean age of 48, 47% female, mean BMI 36.6) for a mean of 4.2 years, overall complications were relatively infrequent for both groups, with a total of five reoperations (2 vs. 3 for BPD) and seven readmissions (3 vs. 4 for BPD), though occurrences were again less common for RYGB patients. The final RCT (Mingrone, 2012) evaluated 60 patients (mean age 43, 53% female, mean BMI 45.2) over two years and found that the number of reoperations was similar (1 in each group), but more overall complications occurred in patients undergoing BPD (6 vs. 3) compared to RYGB. One patient in each group died across all three studies.

Other Surgical Comparisons
Data were limited for other surgical comparisons. We identified no good quality RCTs and only one fair quality RCT (Himpens, 2006) comparing LAGB to VSG. Of the 40 patients (mean age 38, 80%% female, mean BMI 38) who were followed for up to three years in this study, those in the LAGB group experienced more overall complications (16 vs. 6 for VSG), including nine reoperations compared to four in the VSG group. Among those who required additional surgical intervention, four who underwent LAGB had a conversion to RYGB, while two conversions to BPD were required in the VSG group. As with many other comparative studies, the sample size was too small to detect significant differences between groups, and mortality was not reported.

Prospective Cohort Studies

All prospective comparative cohorts with harms data were of fair or poor quality, with the exception of one (Bowne, 2006). This study evaluated 106 super obese patients (mean age 42.5, 80% female, mean BMI 56) allocated to receive either RYGB or LAGB and followed for a median of 16.2 months. Although RYGB was associated with more early complications (11 vs. 3 for LAGB), the difference was not statistically significant. However, after the first 30 days through the end of the study period, there was a significantly greater incidence of late complications in the LAGB group relative to RYGB (43 vs. 11, p<0.05), including reoperations (15 vs. 3, p=0.04). One patient died in the LAGB cohort following elective band removal.

One prospective study (Hutter, 2011) of fair quality compared three of the four procedures of interest (RYGB, VSG, and LAGB), and had a larger sample size than all the other fair quality prospective studies combined. A total of 28,616 patients (mean age 45.2, 77% female, mean BMI 46.2) were evaluated over a period of one year; the study only reported on complications within the 30-day perioperative period, however. Thirty-day morbidity was highest in the open RYGB group (14.98%), followed by laparoscopic RYGB (5.91%), VSG (5.61%), and LAGB (1.44%). Thirty-day reoperation rates followed the same pattern (5.06%, 5.02%, 2.97%, and 0.92% for the four procedural approaches), as did 30-day rate of hospital readmission (9.41%, 6.47%, 5.40%, and 1.71%). Overall, both laparoscopic RYGB and VSG had significantly higher risk-adjusted morbidity, readmission, and reoperation rates compared to LAGB, but VSG had a significantly lower risk-adjusted reoperation rate compared to laparoscopic RYGB. Perioperative mortality ranged from 0.08% to 1.1% across groups, but rates did not statistically differ between them.

Retrospective Cohort Studies

Of the 59 retrospective cohort studies that reported on harms of surgery, only four were considered to be of good quality (Campos, 2011; Carlin, 2013; Galvani, 2006; Arterburn 2014). One of these studies (Carlin, 2013) evaluated almost 9,000 patients (mean age 46, 74% female, and mean BMI 47.5) over a three-year period and compared three of the four bariatric surgery procedures of interest – RYGB, LAGB, and VSG. Data from an externally audited, statewide clinical registry in Michigan was reviewed for overall complications, reoperations, and mortality, with each group matched on multiple baseline variables. There were significant differences between groups, with RYGB generating the highest overall complication rate (10.0% vs. 2.4% and 6.3% for VSG and LAGB respectively, p<0.0004). RYGB also had significantly higher major complication and reoperation rates compared to LAGB, but these measures did not differ in comparison to VSG. Mortality was comparable among the three groups (0.10%, 0.07%, and 0.07% for RYGB, LAGB, and VSG, respectively). These complications are only reported for the perioperative period, however, due to substantial patient attrition.

Another very large retrospective cohort of fair quality (Nelson, 2012a) identified 78,951 patients (mean age 45, 78% female, mean BMI 48) from the Bariatric Outcomes Longitudinal Database (BOLD) undergoing BPD or RYGB. Reoperation rates were significantly higher for BPD (11.5% vs. 7.2% for RYGB, p<0.001), most of which occurred during the perioperative period. The rate of overall complications was higher for BPD patients as well, with patients experiencing significantly higher rates of infection (6.6% vs. 3%) and nutritional deficiencies (4.1 vs. 2.1) compared to RYGB (p<0.001 for both outcomes). In addition, the mortality rate was significantly higher in the BPD group compared to RYGB (1.2% vs. 0.3%, p<0.001). As with previously reported studies, rates of follow-up were poor with only 27% and 28% in the RYGB and BPD cohorts remaining in the study at the end of one year.

Table 5 on the following page represents the median complication, reoperation and mortality rate across all retrospective comparative studies of good or fair quality. 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 Appendix D) with VSG representing the lowest complication rate (3.9%), LAGB with the highest reoperation rate (7.4%), and BPD with the highest overall complication rate (26.9%).

Table 5: 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.

BPD = Biliopancreatic Diversion, LAGB = Laparoscopic Adjustable Gastric Banding, RYGB = Roux-en-Y Gastric Bypass, VSG = Vertical Sleeve Gastrectomy

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 (2 for BPD, 7 for LAGB, 3 for RYGB, and 0 for VSG) met this criteria for inclusion due to inconsistent reporting of complications and substantial sample attrition. Although not discussed here, data abstracted from these studies can be found in Appendix D.

Harms of Bariatric Surgery in 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 adverse events, of which eight were hospital admissions due to depression or hypertension. Twelve patients experienced 13 adverse events 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 8 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. There was only one death due to cardiac failure during the study period which occurred in the RYGB group.

A large poor-quality retrospective cohort (Lennerz, 2014) evaluated 345 patients (mean age 19, 67% female, mean BMI 47.4) between 8-21 years old who received either RYGB, LAGB, or VSG. Although rates of intraoperative and general postoperative complications were comparable between groups, specific post-operative complications (e.g., surgical revision, blood transfusion, sepsis) occurred more frequently in the VSG group (9.1%) than either the RYGB (5.2%) or the LAGB groups (2.5%) (p=0.019). However, these results should be interpreted with caution given that only 48% of the original population were available for follow-up. No deaths occurred during the study period.

One case series (Silberhumer, 2011) met all our criteria for inclusion and reported data on harms. The authors evaluated 50 adolescent patients (mean age 17.1, mean BMI 45.2) undergoing LAGB with up to seven years of follow-up. Band-related complications occurred in six patients, all of which occurred after 26 months, and one of these patients underwent conversion to RYGB. Six additional patients were also converted to RYGB due to treatment failure (i.e., EWL <50%), of which three had reappearance of comorbidities. Four additional case series (Boza, 2012; Nadler, 2008; Raziel, 2014; Nocca, 2014) which met our inclusion criteria for sample size and mean duration of follow-up also reported on the harms of surgery. The most common complication reported across all studies was reoperation, which was more common for those undergoing LAGB (17 vs. 4 for VSG). Mortality was either not reported or no deaths occurred. Study details on these case series can be found in Appendix D.

> **Key Question #4**: What is the differential effectiveness and safety of bariatric surgery procedures according to health-system and/or program factors such as:
>
> a.   Surgeon experience
> b.   Procedure volume
> c.   Certification of surgery center
> d.   Members of core team
> e.   Type of pre-procedure preparation/post-procedure support

Surgeon experience has been primarily assessed through 'learning curve' studies in which patients are stratified into consecutive groups in order to compare outcomes between the first cohort receiving a particular procedure with later groups. Most learning curve studies have reported outcomes for RYGB patients; we found no studies related to BPD/DS. Operative times, complication rates, and length of hospital stay appear to decrease over time for RYGB, LAGB, and VSG, but results vary by surgeon and institution. Many studies report an inverse relationship between hospital/surgeon volume and adverse events, but concerns that sampling effects in low-volume settings may inflate estimates of harm have been voiced. Evidence is inconsistent as to whether accredited centers improve outcomes after bariatric surgery. It has been difficult to determine whether differential outcomes result from the volume requirements of certification, other standards of certification, or if effects are falsely inflated by smaller samples in non-accredited low volume facilities. There are very few studies that address members of the core team in relation to bariatric surgery outcomes. Two studies found that multidisciplinary teams reduce complications and improve chances for successful weight loss. Finally, the majority of studies related to pre-operative weight loss and support groups report that these interventions do not improve post-operative weight loss or resolution of comorbidities. Post-operative support groups, however, have been shown to help patients make positive lifestyle changes, improve psychological comorbidities, and achieve greater weight loss.

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 stratify patients into consecutive groups and compare 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 biliopancreatic diversion 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.

RYGB

Although it is a technically demanding procedure, implementation of RYGB as part of a surgical training fellowship has been shown to be safe under the supervision of an experienced surgeon. Among bypass patients, fellowship training programs have been credited with shortening operative times and improving perioperative outcomes during a surgeon's early experience with the procedure (Gonzalez,

2007; Iordens, 2012; Oliak, 2004). Gonzalez, Nelson, and Murr (2007) and Oliak, Owens, and Schmidt (2004) found that fellowship training programs reduced operative times by 33-35%.

During the initial learning phase, operative times vary tremendously according to individual facilities and surgeons. Despite individual and institutional variation, learning curve studies almost invariably report significant decreases in operative time, length of hospital stay, and complications between early and later consecutive cases (Pournaras, 2010; Chen, 2012; Ballesta-Lopez, 2005; Huang, 2008; Shikora, 2005; Søvik, 2009; Andrew, 2006; Schaeffer, 2008; Schauer, 2003; Papasavas, 2002). In one of the larger learning curve studies of 750 patients, Shikora and colleagues found that the mean operating time decreased from 212 to 132 to 105 minutes in cases 1-100, 101-200, and 201-300, respectively (Shikora, 2005).

VSG

We found four studies that measured patient outcomes in relation to surgeon experience with laparoscopic VSG (Daskalakis, 2011; Prevot, 2014; Zachariah, 2013; Zacharoulis, 2012). Daskalakis et al. (2011) compared the outcomes of VSG patients who were operated on by surgeons with varying levels of experience. The researchers found that rates of overall and major complications did not differ among individual surgeons or between the early and late period of experience for the three surgeons. However they did notice that the mean operating time decreased from 68 minutes to 54 minutes after the first 115 cases (p<0.001).

The remaining sleeve gastrectomy learning curve studies followed the first consecutive patients (sample size ranged from 84 to 228 cases) to undergo sleeve gastrectomy at the authors' respective institutions and stratified patients into two or three groups of 28-50 according to case sequence (Prevot 2014; Zachariah 2013; Zacharoulis 2012). Prevot et al. (2014) not only found a significant reduction in operative time after the first 28 cases (138.8 minutes vs. 93 minutes in the following 28 cases, p<0.01), but also a greater percentage of excess weight loss after 5 years (33.6% vs. 47.9%, p=0.042). In a study of the first 102 VSG cases at their institution, Zacharoulis et al. found significant reductions in operative time and length of hospital stay after a threshold of 68 cases (Zacharoulis, 2012). While Zachariah and colleagues did not find a reduction in operative time or hospital stay over time, they did find that the overall complication rate declined from 8% to 1.68% (p=0.022) after the first 50 patients (Zachariah, 2013).

LAGB

We identified two studies that compared outcomes among LAGB patients across consecutive series (Shapiro, 2004; Breznikar, 2009). Similar to the findings for other procedures, researchers found that operative time and the overall number of complications reduced as surgeons' experience grew over time. For example, Shapiro and colleagues found that mean operating time reduced from 79 minutes to 59 minutes after the first 30 cases (p=0.004) and the complication rate fell from 37% to 7% (p=0.005) (Shapiro, 2004).

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 adverse events. 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 a RYGB operation was significantly higher at low volume hospitals ($13,908 $\pm$ $9573 versus $10,292 $\pm$ $6680 for high-volume, p<0.01).

Findings were similar in other large studies. Birkmeyer and colleagues (2010) found serious complication rates among Michigan patients of 4.1% (95% CI 3.0%, 5.1%), 2.7% (95% CI 2.2%, 3.2%), and 2.3% (95% CI, 2.0%, 2.6%) in low (<150 cases/year), medium (150-299 cases/year), and high volume hospitals ($\geq$300 cases/year), respectively (p<0.001). Based on data from the U.S. Nationwide Inpatient Sample for open and laparoscopic bariatric procedures, Gould et al. (2011) found that each incremental increase in volume of 25 cases yielded lower complication and mortality rates without an obvious threshold for best performance (Gould, 2007).

Murr et al. (2007), used the Florida-wide hospital discharge database to analyze the mortality and hospital volume relationship among gastric bypass patients, and found that mortality was lowest (0.1%) in the hospitals where 100-199 procedures were undertaken over a 5-year period compared to low volume (<10 procedures) hospitals (2.9%) and high volume hospitals (0.3%) in which more than 500 bypass procedures were performed. Hospitals in the 100-199 range also had the lowest complication rate (5%). The authors concluded that a threshold of 100-199 procedures over a five-year period might be an appropriate performance threshold.

The relationship between low volume facilities and poorer outcomes seems to hold true when considering hospital volume and surgeon volume together. Torrente and colleagues (2013) used gastric bypass data from the Pennsylvania Health Care Cost Containment Council to assess both surgeon and hospital volume. They found that low-volume surgeons (<50 cases per year) at low-volume hospitals (< 125 cases per year) had poorer outcomes, with 0.57% of patients dying in the hospital compared to high-volume surgeons (>50 cases per year) at high-volume hospitals (300 or more cases per year) (in-hospital mortality: 0.12%). Data from the Michigan Bariatric Surgery Collaborative registry reveal a similar trend in serious complication rates, which were about twice as high for low-volume surgeons (<100 cases per year) at low-volume hospitals (<150 cases per year) than for high volume surgeons ($\geq$250 cases per year) at high-volume hospitals ($\geq$300 cases/year) (Birkmeyer, 2010). Finally, Weller and colleagues used discharge data in New York to assess differences in readmission rates, and found patterns similar to those described above (Weller, 2007).

Smith et al. (2013) note that technical factors may partially explain why high-volume surgeons (>100 RYGBs/year) have better results. Analyzing data from the Longitudinal Assessment of Bariatric Surgery (LABS), which included 3,412 RYGB procedures performed by 33 surgeons, Smith and colleagues calculated the relative risk of a composite endpoint, which was comprised of death, venous thrombosis, pulmonary embolism, reoperation, and nondischarge at 30 days, in relation to a number of intraoperative factors. The authors' findings indicate that high-volume surgeons are more likely to perform a linear stapled gastrojejunostomy (58% vs. 16%), use fibrin sealant (61% vs. 30%), and place a drain at the gastrojejunostomy (24% vs. 13%) during RYGB compared with low- volume surgeons (<25

RYGBs/year, p<0.0001 for all comparisons listed). However, after adjusting for these technical factors, the strength of the volume-outcome relationship was reduced from a relative risk of 0.93 to 0.90 per 10 RYGB/year. This suggests that technique alone cannot account for the volume-outcome relationship.

Despite the evidence that a higher volume of procedures produces 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 tend to disappear (Livingston, 2007).

Certification

On February 21, 2006, the Centers for Medicare and Medicaid Services (CMS) released the National Coverage Determination (NCD) for Bariatric Surgery for Treatment of Morbid Obesity. This measure restricted coverage of bariatric surgery to procedures performed at facilities that were accredited by either the American College of Surgeons (ACS) as a "Level 1 Bariatric Surgery Center" or the American Society for Metabolic and Bariatric Surgery (ASMBS) as a "Bariatric Surgery Center of Excellence (COE)."

The effects of the NCD on health outcomes have proven challenging to measure, with many studies showing no or marginal differences. In a retrospective longitudinal study of 2004-2009 hospital discharge data from 12 states, Dimick et al. (2013) compared bariatric surgery outcomes before and after the NCD's publication in both Medicare and non-Medicare patients (n=321,464). While complication and reoperation rates improved during the study period in both groups, this trend was already occurring prior to the coverage decision. After controlling for time trends, patient factors, and changes in procedure type (to account for a shift away from open RYGB to laparoscopic RYGB and LAGB), there were no statistically-significant changes in outcomes after the NCD. For example, the complication rate was 8.0% after the NCD vs. 7.0% before (relative risk 1.14, 95% CI: 0.95, 1.33) (Dimick, 2013).

Evidence suggests that the impact of the NCD may have been more social than clinical, including unintended consequences for minority populations (Nicholas and Dimick, 2013). Nguyen et al. (2010) observed an initial 29.3% reduction in the number of procedures performed among Medicare patients, although these numbers eventually surpassed baseline levels within two years after the NCD's publication. Restricting care to accredited facilities was also associated with a relative decline in the proportion of nonwhite Medicare patients receiving bariatric surgery (Nicholas and Dimick 2013). Furthermore, Livingston et al (2010) observed that the median distance Medicare patients were required to travel to receive care at a COE increased from 25 miles to 46 miles after publication of the NCD.

Other studies have sought to determine whether accreditation improves clinical outcomes. Livingston (2009) used the 2005 National Inpatient Survey from the Healthcare Cost and Utilization Projects (HCUP-3) to compare outcomes at COE-designated and non-designated programs. The author reported that both the hospital mortality rate and complication rate did not statistically differ between COEs and non-

COEs (Livingston, 2009). Similarly, Birkmeyer et al (2010) did not find significant differences between adjusted rates of serious complications between COE hospitals and non-COE hospitals.

In contrast to the findings stated above, Nguyen and colleagues evaluated outcomes for bariatric procedures performed at academic centers with COE status vs. non-accredited academic centers in nearly 36,000 patients (Nguyen, 2012). In-hospital mortality (0.06% vs. 0.21%, p=0.003) and hospital length of stay (2.4 vs. 2.7 days, p<0.001) differed significantly in favor of accredited centers, and overall hospital costs were also lower. However, the authors noted that they were unable to determine conclusively whether the findings observed in the study were due solely to accreditation, procedure volume, or a combination of both.

In an attempt to account for these uncertainties, Jafari and colleagues (2013) used the HCUP-3 Nationwide Inpatient Sample to analyze risk-adjusted outcomes for RYGB and VSG cases in accredited (n=216,000) versus non-accredited (n=20,219) high-volume centers ($\geq$ 50 cases annually). The authors found that non-accredited centers were associated with higher rates of in-hospital mortality (OR 3.57; 95% CI: 1.49, 8.33) but lower rates of serious morbidity (OR 0.84; 95% CI: 0.71, 0.98) (Jafari, 2013). The in-hospital mortality rate of high-volume non-accredited centers was comparable to that of low-volume centers (0.22 vs. 0.17%, respectively), suggesting that the standards associated with accreditation were more important predictors of outcome than annual case volume.

In April 2012, the ASMBS and the ACS formed the Metabolic Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP). This unified national accreditation program maintained many of the standards of the previous programs, but adjusted volume requirements to 50 or more cases per year. Despite this change, CMS removed the requirement that bariatric surgical procedures be performed at an accredited facility in September 2013, citing evidence that outcomes were comparable at accredited and non-accredited facilities (CMS, 2013).

Members of Core Team

Very few studies have examined the differential effectiveness of multidisciplinary care across the various bariatric procedures. This is most likely because multidisciplinary care is required for accreditation as a COE; the team generally includes nutritionists, psychologists, pulmonologists, cardiologists and other medical specialists trained in bariatric care. In a nationwide 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 analyzed 2-year predictors of success, which they defined as EWL>50% (Chevallier, 2007). The authors found that patients who did not change their eating habits after surgery were 2.2 times less likely to have weight loss success (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). Although they did not directly measure the effects of a multidisciplinary team, the authors emphasized that these findings were indicative of the need to employ a multidisciplinary team before and after the operation (Chevallier, 2007).

Furthermore, a team approach, as compared to a single surgeon approach, may reduce operative times and shorten hospital stays among patients undergoing laparoscopic RYGB (Chen 2012).   We found a single study that compared outcomes between 200 RYGB patients who either received care through a multidisciplinary team approach or from an individual surgeon (mean age 31, 62% female, mean BMI 43 kg/m^2) (Chen, 2012). Twelve months post-surgery, patients treated by the multidisciplinary team lost a greater percentage of overall weight than those treated by an individual surgeon (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 group. As mentioned in Key Question 2, the authors credited these improved outcomes to regularly scheduled appointments with a specialized dietician as well as to surgeons being given more time to focus on improving their technique.

Type of Pre-procedure Preparation/Post-procedure support

Pre-operative interventions such as dietary counseling or weight loss programs are mandated by a growing number of insurance payers despite a lack of evidence that these measures improve outcomes. An RCT of 55 patients (mean age 46, 83.5% female, mean BMI 45.5 kg/m^2) who were randomized to participate in a medically supervised weight management program in the six months prior to LAGB surgery did not produce significant differences in post-operative weight loss from those who received usual pre-operative care (Parikh, 2012).

In another RCT, 100 patients (mean age 44, 84% female, mean BMI 49 kg/m^2) were randomized to either lose 10% of their body weight or not prior to gastric bypass (Alami, 2007). Although the researchers reported greater short term (3 month) EWL in the weight loss group (44.1% vs. 33.1%; p=0.0267), these differences were no longer significant by 6 months of follow-up (53.9% versus 50.9%; p=NS). Moreover, major complications, intraoperative complications, conversion, and resolution of comorbidities were not significantly different between groups, although the weight loss group had on average a 37.4-minute shorter operative time.

A third RCT, which randomized 298 patients (mean age 40, 70% female, mean BMI 43 kg/m^2) to receive a two-week very low calorie diet (VLCD) or no diet prior to RYGB, had slightly different results (Van Nieuwenhove, 2011). Although operative times and intraoperative complications did not differ between groups, the authors did observe significant differences in 30-day morbidity (8 in VLCD vs. 18 in controls, p=0.04).

Despite the possibility that pre-operative weight loss reduces 30-day morbidity, the majority of available cohort studies indicate that these programs do not correlate with post-operative weight loss. In a retrospective analysis of 539 patients receiving gastric bypass, banding, or sleeve gastrectomy, Becouarn, Topart, and Ritz (2010) did not find a relationship between pre- and post-operative weight loss, regardless of the surgical technique performed. They suggest that while pre-operative weight loss can reduce the difficulties of surgery, the advantages for long-term weight loss are not validated. Correspondingly, three retrospective analyses of RYGB patients who participated in pre-operative weight loss programs found that these programs were not associated with better excess weight loss 1-2 years after the surgery (Carlin, 2008; Harnisch, 2008, Huerta, 2008) or with resolution of comorbidities (Harnisch, 2008). Of note, another cohort study documented potentially negative consequences of mandated pre-operative weight loss: Jamal and colleagues (2006) found that the pre-surgery dropout rate among 322 RYGB patients was 50% greater in a group whose insurance mandated that patients participate in 13 weeks of pre-operative dietary counselling compared to patients without such a requirement (p<0.05).

A single study of 548 patients, which retrospectively stratified results by percentage of pre-operative weight loss, found that patients who lost more than 10% of their weight prior to surgery had greater excess weight loss 12 months after RYGB than patients who lost less than 5% (72.7% vs. 63.1%, p=0.015) (Giordano, 2014). However, the authors of this study identified several limitations that may have biased the results, including imbalance in demographic and clinical characteristics between weight-loss groups,

variable pre-operative weight loss methods, lack of control for site/surgeon effects, and attrition of the sample (loss to follow-up was identified as a limitation but the rate was not reported).

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). Gould and colleagues 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) (Gould, 2007).

Although pre-procedure support groups have shown little success in improving post-operative lifestyle changes (Lier, 2012), 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 excess weight loss (80% versus 64%; p<0.001) and BMI reduction (6.48 vs. 3.63, p<0.001) (Nijamkin, 2012).

Key Question #5: What is the differential effectiveness and safety of bariatric surgery procedures according to patient and/or clinical factors such as:

- a.   Age
- b.   Gender
- c.   Race/ethnicity
- d.   BMI
- e.   Presence of comorbidities
- f.   Prior event history
- g.   Smoking status
- h.   Psychosocial health
- i.   Pre/post procedure adherence with program recommendations

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/clinical factors is largely inconclusive. There is some evidence that patients in older age categories experience fewer complications when undergoing LAGB compared to VSG or RYGB. Evidence of different weight and complication outcomes is inconsistent when stratified by gender. Although males tend to have higher rates of overall complications, one study found a higher prevalence of long term complications among female LAGB patients compared to male LAGB patients. A statistical difference in long term complications was not found for RYGB males and female. Outcomes are rarely stratified by race/ethnicity, and comparisons are confounded by different body composition in some racial categories (e.g., Asian vs. European/Caucasian). Patients in higher BMI categories are more likely to experience longer operative times and hospital stays; while these patients tend to lose a higher percentage of pre-operative BMI than those in lower BMI categories, the percentage of excess weight loss appears to decline as BMI increases. Studies of patients with BMI <35 are growing in number and have primarily focused on resolution of type 2 diabetes. Rates of complications and post-surgical hypothyroidism are greater for hypertensive patients undergoing RYGB than LAGB. Other comorbidity data are inconclusive. Adherence to pre- and post-operative programs may improve post-surgery weight loss for LAGB patients, but appears to have a neutral impact on RYGB patients. We found no studies that stratified outcomes by prior event history, smoking status, or psychosocial health that met our inclusion criteria.

There is a paucity of RCTs and prospective comparative cohort studies comparing the differential effectiveness of specific bariatric procedures on various patient subgroups. Available studies have been relatively inconsistent in reporting, defining, and measuring outcomes for key subgroups. As such, evidence about the differential effectiveness and safety of bariatric surgery procedures according to patient/clinical factors is largely inconclusive. Given the scarcity of such data, we have included retrospective and lower-quality studies in the sections that follow. Results should be interpreted with caution.

Age

Older patients are more susceptible to complications and may not lose as much excess body weight as their younger counterparts. In a matched cohort study of 8,847 patients (mean age 46, 74% female, mean BMI 48), Carlin et al. (2013) examined 30-day serious complications by age category and found that, across all procedures, serious complications increased in patients over 50 years of age relative to patients in younger age categories.   When individual procedures were compared, rates of serious complications did not statistically differ between RYGB and VSG. However, when VSG and LAGB were compared, rates were significantly higher among VSG patients starting at age 40 and above.

Pohle-Krauze and colleagues found a differential effect on LDL cholesterol by age group in a retrospective comparison of 294 RYGB and LAGB patients (mean age 45.6, 84% female, mean BMI 47) (Pohle-Krauza, 2011).   Between baseline and 42 months postoperatively, LDL cholesterol significantly decreased in RYGB patients aged 47 and above, while LAGB patients of the same age experienced a non-significant _increase_ in LDL levels. Differences in LDL cholesterol values were not statistically-significant in patients younger than 47 for either procedure.

Gender

Studies that stratified outcomes by both gender and procedure type did not report consistent weight-loss patterns. For example, Nguyen et al. (2013), found no differences in weight loss between genders during the first three years after RYGB or LAGB but did note that LAGB males had a greater reduction in BMI than females receiving the same procedure beyond three years (-8.2 versus -3.9 kg/m^2, p= 0.02). Among adolescents receiving these same procedures, Messiah et al. (2013) found that RYGB resulted in a BMI percentile decrease approximately twice that of LAGB among boys (-3 vs. -1.5 percentile points) but more than _four_ times that of LAGB among girls (-9 vs. -2) after one year of follow-up. Breznikar et al. (2009) reported EWL after one year of follow-up and noted that female adults had a greater mean EWL than males after LAGB (54% versus. 40.9% respectively) but not after VSG (52.1% versus 65.7%), although the significance of these differences was not reported. Similarly, Bekheit (2014) found a significant difference in EWL between 35 male and 254 female LAGB patients (males: -0.59% vs. females: 36.9%, p=0.002) but similar rates of EWL by gender among those undergoing RYGB (Bekheit, 2014).

As discussed in Key Question 2, males tend to have higher complication rates than females. However when outcomes are stratified by both gender and procedure type, the evidence is rather inconsistent. For example, in a retrospective study that compared 1,295 RYGB and LAGB patients (mean age 40, 81% female, mean BMI 43.6) Nguyen NQ et al. (2013) reported similar rates of longer-term complications in male and female RYGB patients but not in male and female LAGB patients: longer-term complications were shown to be far less likely in male LAGB patients than female LAGB patients (male: 2/131 [1.5%] versus female: 59/555 [10.6%], p <0.001).

Race/Ethnicity

We found a single study that stratified outcomes by race/ethnicity. Although it was not included in our formal review, we include it here as the only study that stratified outcomes by both race and procedure type. In an analysis of New York's inpatient hospital discharge database, Lindsey et al. (2009) identified 8,413 adults who underwent RYGB or LAGB during calendar year 2006. The authors found statistically significant differences in complication rates across race/ethnicity categories for LAGB patients (2.6% for white or black non-Hispanic, 3.9% for Hispanic, and 6.3% for other/unknown [Asian, Native American, Hawaiian/Pacific Islander], p<0.001) but no differences among those undergoing RYGB.

Four studies were conducted exclusively on Asian populations (Lee, 2010; Liang, 2013; Wong, 2009; Yong, 2012). Previous studies have ascertained that certain Asian populations have a higher percentage of body fat than white or European populations as well as a higher prevalence of both type 2 diabetes and cardiovascular risk factors in levels of BMI lower than those classified by the World Health Organization (WHO) as overweight or obese (WHO, 2004). Because of the disparities between Asian and European body composition, some Asian investigators performed surgery on patients at lower levels of BMI than is typical of U.S. or European studies (i.e., ≥40 or ≥35 with comorbidities). The four studies meeting our inclusion criteria from Asian populations had baseline BMIs between 30 and 42 and were followed for 6-36 months. The RYGB patients in Lee's study experienced greater excess weight loss compared to five other studies of RYGB patients from Europe or the United States (83% vs. 52-75%) that had similar durations of follow-up and baseline BMI (Cutolo, 2012; Leslie, 2012; Puzziferri, 2008; Vidal, 2013; Weber, 2004). However when compared to LAGB patients from U.S. or European studies, the patients in Lee et al.'s study experienced less excess weight loss (30% vs. 42-79%) (Dixon, 2012; O'Brien, 2010; Puzziferri, 2008; Sabbagh, 2010; Weber, 2004). Because the other Asian studies included in our review either did not report EWL, did not report baseline BMI, or did not have comparative lengths of follow-up with any non-Asian studies, it is impossible to comment whether Lee et al.'s findings are consistent across other Asian patients.

BMI

Patients with higher preoperative BMIs experience lower levels of excess weight loss than patients with lower preoperative BMIs. For example, in a retrospective comparative cohort study of 1,261 patients, Biertho and colleagues found that after 18 months follow-up, EWL for patients with a BMI between 50 and 60 was 69% and 33% among RYGB and LAGB patients, respectively (Biertho, 2003). Patients with lower preoperative BMIs (between 40 and 50) experienced greater EWL for both procedures, but the difference between them also widened somewhat (81% and 40%, respectively).

Similarly, Puzziferri et al.'s (2008) prospective cohort study reported that over two years, mean excess weight loss was greater for those who had a preoperative BMI <50. RYGB patients who had a preoperative BMI >50 had 0.12 times the odds of successful weight loss (EWL >40%) after 6 months postoperatively than those with a preoperative BMI of 50 or below (95% CI: 0.08, 0.18). LAGB patients with a preoperative BMI greater than 50 followed the same pattern, with a 0.13 odds ratio of successful weight loss (95% CI: 0.06, 0.29). Although this effect diminished over time among RYGB patients and was no longer statistically significant after 18 months of follow-up, LAGB patients with a higher pre-surgical BMI remained significantly less likely to have successful weight loss (OR 0.43; 95% CI: 0.24, 0.78). One study stratified procedure-related parameters by BMI category and procedure type (Stephens, 2008). The authors found that length of hospital stay was significantly longer for RYGB patients with a baseline BMI >60 relative to RYGB patients with a starting BMI <60 (3 vs. 2 days hospital stay, p<0.05), but that operative time did not significantly differ. These measures did not statistically differ by BMI category among LAGB patients.

The RCTs and comparative cohorts evaluated in this assessment are summarized in **Table 6** on pages 64-65 according to the mean baseline BMI reported in each study and the median values of six outcomes related to surgical success (% change in BMI, %EWL, and improvement/resolution of type 2 diabetes, hypertension, dyslipidemia, and sleep apnea). While the evidence presented in this table indicate certain trends, it should be interpreted with caution as the reported medians are composites of good, fair, and poor quality studies. Also, given that studies did not use a uniform definition for improvement or resolution of comorbidities, the results should be interpreted with caution.

Comparative Studies in Patients with BMI <35

A growing number of comparative studies have focused on patients with more moderate levels of obesity (i.e., BMI <35), with accordingly increased interest in this population among clinicians and payers. Among our set of good- and fair-quality RCTs and prospective cohort studies, a total of nine enrolled patients with BMIs at this level (Courcolas, 2014; Dixon, 2007; Dixon, 2008; Halperin, 2014; Ikramuddin, 2013; Kashyap, 2013; O'Brien, 2006; Schauer, 2012; Scopinaro, 2011). A tenth RCT (Liang, 2013) is not included in this discussion because it was performed in China; differences in body composition and fat distribution between Asian and Western populations are discussed on the previous page.

Importantly, seven of the ten studies included presence of type 2 diabetes 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 **Table 6** on the following page; 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 involving lower BMI levels (including those with a mean preoperative BMI slightly above 35) that measured complete type 2 diabetes 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 diabetes (e.g., reduced HbA1c, reduced insulin use) showed between-group differences of even greater magnitude.

Table 6: Outcomes by baseline mean BMI category

		Baseline Mean BMI Category							
		30-34.99		**35-39.99**		**40-49.99**		**>50**	
		Median	**Range**	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
% Decrease BMI	RYGB	25.4	(19.6-34.3)	26.0	(24.1-33.1)	32.2	(7.5-52.3)	34	(10.1-46.7)
	VSG	21.3	(21.3-21.3)	22.0	(19.1-22.5)	28.4	(15.0-37.1)	30.1	(11.0-39.4)
	LAGB	16.8	(11.8-21.7)	16.8	(13.0-17.5)	20.4	(6.0-46.8)	17.7	(1.0-31.8)
	BPD/DS	31.8	(17.3-46.3)			32.6	(15.9-50.8)	43.4	(39.2-47.7)
	Follow-up (months)	12.0	(3.0-45.2)	15.3	(12.0-60.0)	12.0	(0.5-120.0)	22.6	(1.2-84.0)
	No. Studies	7		6		79		22	
	Good/Fair/Poor	2/3/2		3/1/2		9/34/36		4/10/8	
% EWL	RYGB	70.0		77.0	(61.0-92.9)	67.0	(27.1-88.0)	61.8	(43.8-72.3)
	VSG			58.5	(51.0-66.0)	59.2	(30.7-83.0)	47.5	(25.4-75.0)
	LAGB	87.2		50.1	(34.0-62.5)	43.5	(18.2-78.8)	45.9	(31.0-73.0)
	BPD/DS					52.7	(34.9-70.4)	73.4	63.0-84.0
	Follow-up (months)	18.0	(12.0-24.0)	30.0	(18.7-60.0)	24.0	(0.47-120)	24.0	(12.0-84.0)
	No. Studies	2		4		57		15	
	Good/Fair/Poor	1/0/1		1/1/2		6/27/24		1/8/6	
% Improvement Hypertension	RYGB			90.0		71.0	(22.0-100.0)	62.6	(60.7-69.2)
	VSG					64.3	(23.5-100.0)		
	LAGB			40.0		57.5	(18.0-100.0)	54.3	(33.3-66.7)
	BPD/DS	67.0				81.4	(68.6-87.0)	68.3	(66.7-69.9)
	Follow-up (months)	36.0		60.0		21.0	(3.5-84.0)	24.0	(12.0-50.4)
	No. Studies	1		1		29		5	
	Good/Fair/Poor	0/1/0		0/0/1		4/12/13		1/3/1	

		Baseline Mean BMI Category							
		30-34.99		**35-39.99**		**40-49.99**		**>50**	
		Median	Range	Median	Range	Median	Range	Median	Range
% Improvement T2DM	RYGB	51.1	(33.0-92.3)	73.4	(66.7-80.0)	79.0	(33.0-100.0)	77.1	(40.0-100.0)
	VSG	50.0	(50.0-50.0)			77.3	(36.0-100.0)	88.9	(88.9-88.9)
	LAGB	33.0	(21.1-100.0)	50.0	(25.0-73.0)	50.0	(17.0-100.0)	52.3	(36.4-66.7)
	BPD/DS	84.8	(83.0-84.8)			87.1	(81.5-92.7)	91.4	(82.7-100.0)
	Follow-up (months)	12.0	(3.0-45.2)	24.0	(12.0-60.0)	16.0	(1.0-62.7)	24.0	(1.5-50.4)
	No. Studies	6		3		35		7	
	Good/Fair/Poor	0/3/3		2/0/1		3/14/18		1/4/2	
% Improvement Sleep Apnea	RYGB	89.0				70.5	(10.0-100.0)	56.7	(49.3-88.0)
	VSG					62.0	(6.0-99.0)		
	LAGB					29.0	(3.0-55.0)	46.2	(39.3-66.7)
	BPD/DS	90.0						79.5	(78.9-80.0)
	Follow-up (months)	45.15				21.6	(12.0-36.0)	20.1	(12.0-20.1)
	No. Studies	1		0		11		4	
	Good/Fair/Poor	0/0/1				2/5/4		1/3/0	
% Improvement Dyslipidemia	RYGB			100.0		64.5	(6.0-100.0)	52.9	(27.3-58.8)
	VSG					67.5	(35.0-67.5)		
	LAGB			38.0		36.5	(0.0-36.5)	34.4	(23.3-45.5)
	BPD/DS					90.0	(90.0-90.0)		
	Follow-up (months)			60.0		24.0	(12.0-62.7)	16.2	(12.0-50.4)
	No. Studies	0		1		18		3	
	Good/Fair/Poor	0		0/0/1		2/9/7		1/1/1	

An additional RCT evaluated the effects of LAGB vs. 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). 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, vs. 19% in the nonsurgical group (p<0.05).

Most of these studies also reported improvements in measures of cholesterol and hypertension, 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.

Other Comorbidities
Although many studies reported the prevalence of common obesity-related comorbidities among respective study populations, we found a single study that stratified outcomes according to both comorbidity and procedure type. Lindsey et al. (study characteristics described in race/ethnicity section) found that congestive heart failure and cardiac arrhythmia were associated with higher complication rates for the three procedure types: post-surgical complication rates were 40% for open RYGB, 21.1% for laparoscopic RYGB, and 17.4% for LAGB among patients with congestive heart failure (p<0.001), and 38.8%, 38.7, and 11.7% among those with cardiac arrhythmias (p<0.001); both sets of complication rates were significantly higher than for the overall cohorts (13.4%, 8.6%, and 3.1% for open RYGB, laparoscopic RYGB, and LAGB, respectively). Other comorbidities, including valvular disease, pulmonary circulation disorders, coagulopathy, and current drug abuse, were correlated with a greater risk of complications for open RYGB but not for laparoscopic RYGB or LAGB.

Rates of complications (3.8% vs. 2.3%, p=0.03) and postoperative hypothyroidism (0.9% vs. 3.3%, p=0.04) differed significantly for LAGB vs. RYGB among patients with hypertension at baseline, but did not differ among those without this comorbidity (Lindsey, 2009). Patients with peripheral vascular disorders who underwent RYGB had a significantly greater complication rate than those without this condition (32.0% versus 8.4%, p<0.001), but this difference was not observed among those undergoing LAGB (Lindsey, 2009).

Prior Event History
We found no studies that stratified outcomes by prior event history and met our inclusion criteria.

Smoking Status
We found no studies that stratified outcomes by smoking status and met our inclusion criteria.

Psychosocial Health
We found no studies that stratified outcomes by factors associated with psychosocial health and met our inclusion criteria.

Pre/post Procedure Adherence with Program Recommendations

We found a single retrospective comparative cohort study that stratified outcomes by adherence with pre-/post-operative program recommendations (mean age 43, 87% female, mean BMI 44) (El Chaar, 2011).   The study reported that LAGB patients who missed more than 25% of their pre-procedure appointments experienced 23% EWL at 12 months, compared with 32% for those who missed fewer appointments (p=0.01) (El Chaar 2011).   However, no differences in RYGB performance were observed when stratified by pre-procedure appointment attendance.

Key Question #6: What are the costs and cost-effectiveness of the major bariatric surgery procedures of focus in this evidence review?

Published evidence accumulated to date 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. Findings from our own decision model confirm this, with results that are robust to even extreme assumptions about the durability of treatment effect and the impact of bariatric surgery on mortality. Our model does suggest, however, that bariatric surgery is most cost-effective in morbidly-obese individuals, and that cost-effectiveness erodes somewhat as BMI levels decrease.

Prior Published Evidence on Costs and Cost-Effectiveness

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 quality of life (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 open 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 quality-adjusted life year (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 U.S. populations are summarized in detail on the following page.

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. In 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 the shorter-term (5-year) cost impact of surgery vs. standard care, and 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 $6,600, $17,200, and $6,200 per QALY gained 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).

ICER Simulation Model

In order to augment the available evidence on the economic impact of bariatric surgery, and to compare all procedures of interest in this evaluation, we developed our own decision-analytic model. Where available, we included payment data from the HCA in our evaluation. The focus of attention in our model was on all four procedures of interest (i.e., RYGB, LAGB, VSG, and BPD/DS) in comparison to standard nonsurgical management for all obese individuals (BMI≥30) as well as in subgroups defined by BMI range (i.e., 30-34.9, 35-39.9, and ≥40).

Methods

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 surgery. This analysis compared change in BMI, and proportions of patients with perioperative mortality, reoperation, and medical complications, as well as the proportions of patients with remission of diabetes, hypertension, hyperlipidemia, and sleep apnea. 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, a cost-utility analysis was also conducted over a 10-year time horizon based on assumed trajectories of BMI change after the various forms of surgery and standard care. 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 undergoing surgical treatment for 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 therefore 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: RYGB, LAGB, VSG, and BPD/DS (i.e., with duodenal switch).

Comparator

The reference case analysis compared the various forms of bariatric surgery with conventional weight-loss treatments. Treatments deemed to be conventional included 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 U.S.

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. The model was supplemented by focused literature searches to identify data not provided in short terms RCTs, including resolution of comorbid conditions such as diabetes, hypertension, hyperlipidemia, and sleep apnea. Two main models were constructed: 1) a short-term model using RCT data related to change in BMI, complications and comorbidities at one year; 2) a longer-term 10-year model that includes short-term outcomes from RCTs and incorporates estimates of quality of life, mortality, and comorbid illness using observational study data over 10 years. Note that data on the long-term patterns of comorbidity remission and relapse are scarce; for the longer-term model, we used BMI changes as a proxy for measurement of comorbidity and quality of life over this timeframe.

For the long-term model, a Markov process was used to estimate costs and clinical outcomes in one-year cycles (see **Figure 10** 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/QALYs (for example, BMI and age of survivors).

The model outputs included QALYs, life-years gained, change in BMI, total health care costs, and incremental cost per QALY gained. We performed base case analyses using a Markov cohort analysis and used Monte Carlo simulation for the probabilistic sensitivity analysis.

Given that the four co-morbidities considered will only capture a percentage of health care costs and QALYs given the complexities involved in obesity-related illness and its treatment (Østbye, 2014), 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 solely from these 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). We assumed that standard care (SC), RYGB, VSG, LAGB, and BPD were associated with 3.6%, 26.0%, 24.4%, 19.4%, and 31.2% changes in BMI at one year respectively. After one year, subsequent % changes in BMI 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 keeping weight off (Dolan, 2004). BMI was assumed to remain stable after initial change in standard care recipients (Basu, 2014). Change in BMI is depicted graphically in **Figure 11** on page 73.

Figure 10: Decision model for short and long-term economic outcomes of bariatric surgery
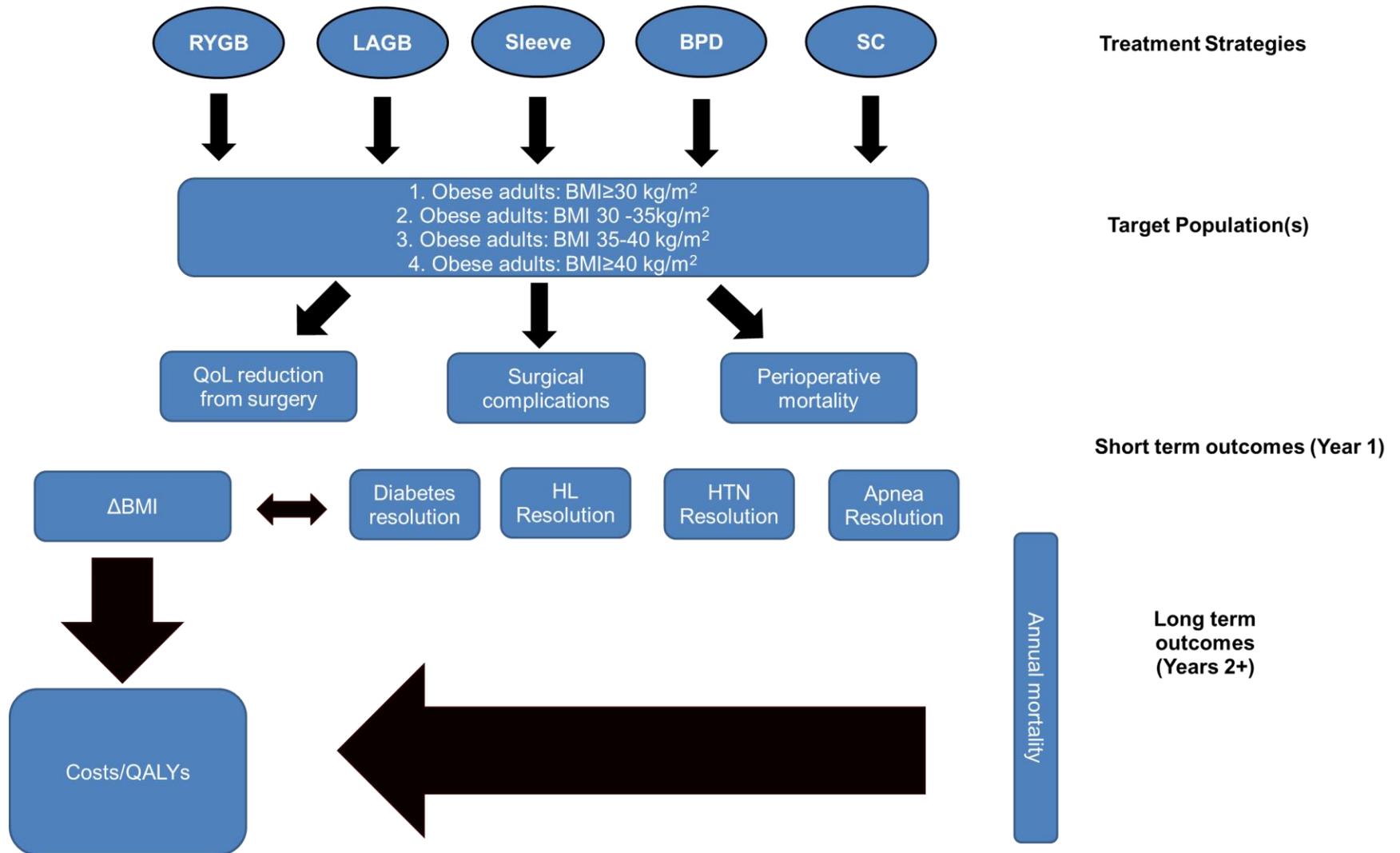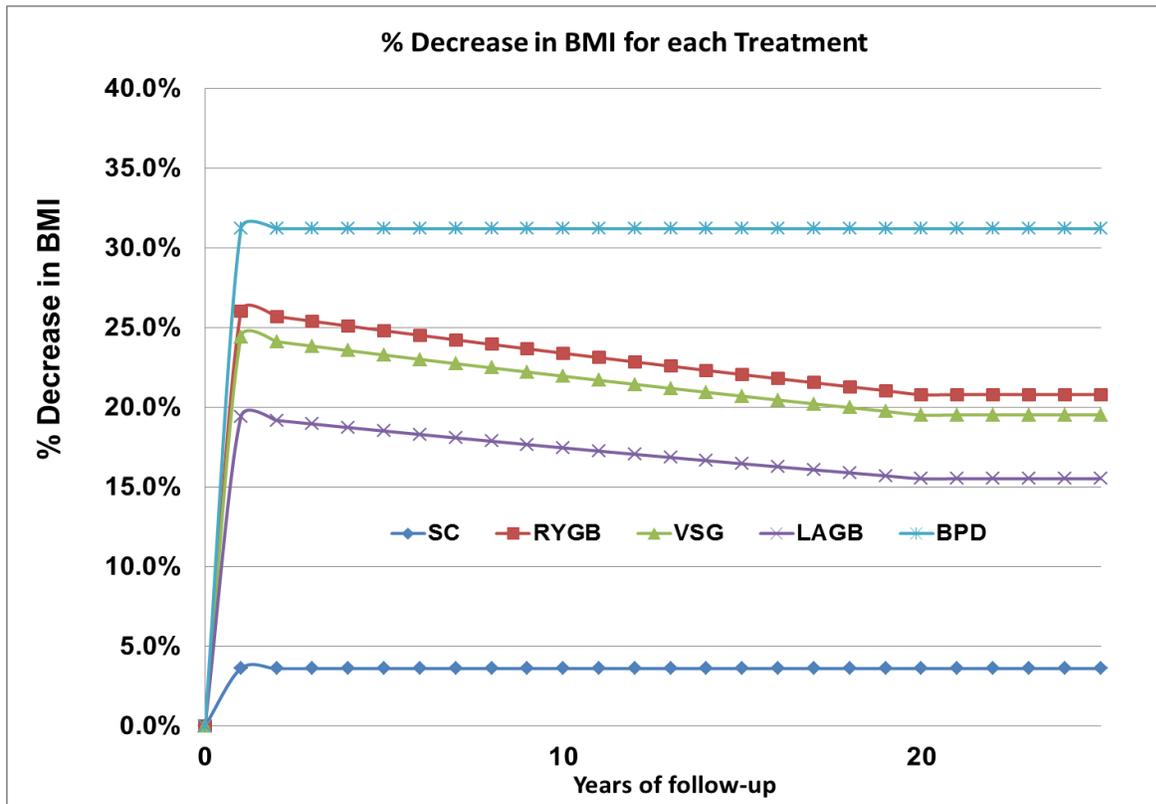
Figure 11: Percentage decrease in BMI by duration of follow-up for treatment strategies in decision model

Mortality

The risk of perioperative mortality among patients undergoing any of the bariatric procedures was 1.35%. 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 were assumed to be associated with relative risks of perioperative mortality of 0.47, 0.52, 0.58, and 1.09 respectively.

The risk of mortality among patients in subsequent years is based on age and BMI (see Appendix E). For standard care, 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 Swedish Obese Subjects study (Sjöström, 2013); given the controversy over this topic, we also conducted alternative analyses assuming no mortality benefit. We did not assume a differential effect on mortality by type of bariatric procedure.

Quality of Life

Improvements in quality of life are thought to be a key benefit of weight loss. We derived the estimates of BMI-specific utilities from a regression analysis of EQ-5D data from 2013 (Rothberg, 2014). In this study, the factors associated with change in health-related quality-of life as assessed by the EQ-5D between baseline and 6-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 health related quality of life as assessed by EQ-5D were as follows:

Δ EQ-5D=0.71995-0.68279*EQ-5D$_{Baseline}$-0.00285*BMI$_{Baseline}$ -0.00957*NoComorb+0.0073*ΔBMI

Based on this, differential gains in health related quality of life will be observed among the various BMI sub-populations considered. For example, patients with more severe obesity (i.e., BMI≥40) will achieve higher gains in health related quality of life than those with less severe obesity (i.e., BMI≥30-34.9) given patients with severe obesity (i.e., BMI≥40) are more likely to have lower health-related quality of life at baseline, more co-morbidities, and achieve more weight loss. A detailed table of our estimates is provided 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 5- and 25-year time horizons via sensitivity analysis.

Complications of Bariatric Surgery

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 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.

For participants undergoing bariatric surgery or subsequent surgery, it was assumed that the quality of life 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.

Estimating Resources and Costs

Direct costs for bariatric procedures were considered from the payer perspective; reimbursement rates from the Washington state Health Care Authority Public Employees Benefits Board were used (see **Table 7** on the following page) where available. Estimates of direct costs included professional and technical fees as well as facility charges for the bariatric surgery procedures. Healthcare costs for short-term complications were derived from the Washington Health Care Authority while other costs at varying levels of BMI were derived from a recently published US study which 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 healthcare expenditures.

Table 7: 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
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%	"

Currency, Price Date, and Conversion

All costs are provided in 2015 U.S. dollars, consistent with the latest available payment data from the HCA.

Analytical Methods

In addition to stratifying results by BMI, several univariate sensitivity and variability analyses were also conducted to explore the impact 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.

Results

Reference Case Analysis – Bariatric Surgery Versus Standard Care (One-year Time Frame)

A change in BMI is a measure of effectiveness for the model using a one-year time frame. This model also includes the complications which occur in year 1. When compared with standard care in all patients with obesity (BMI≥30), the use of RYGB, VSG, LAGB, and BPD/DS was associated with an approximate decrement in BMI of 10.4, 9.8, 7.8 and 12.5 respectively. RYGB, VSG, LAGB, and BPD/DS costs $30,099,

$24,357, $22,035, and $42,979 respectively (see **Table 8** below). 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.

We also stratified results by BMI sub-categories. Overall, the findings for BMI are more favorable for patients with in the morbidly obese category (BMI≥40) compared with those with lower BMI. For example, patients using RYGB and having 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 bariatric surgery procedures. 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. Similarly, resolution of comorbidities was more frequent among those with higher BMI categories. We attempted to gather data related to sleep apnea resolution but data were too limited, particularly when stratified by BMI.

Table 8: Costs and consequences of bariatric surgery and nonsurgical standard care over 1 year of follow-up, among all patients with BMI≥30

Outcome/Cost	Standard Care	RYGB	VSG	LAGB	BPD/DS
BMI≥30					
Clinical Outcome					
BMI loss (mean)	1.44	10.4	9.76	7.76	12.48
Death (%)	1%	2%	2%	2%	2%
Reoperation (%)	0%	6%	3%	12%	7%
Medical complication (%)	0%	11%	13%	2%	21%
Diabetes resolution (%)	2%	14%	14%	13%	18%
Hypertension resolution (%)	4%	19%	23%	17%	19%
Hyperlipidemia resolution (%)	4%	23%	17%	9%	23%
Costs ($)					
Procedure	$3,710	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$787	$402	$1,478	$893
Other Complications	$0	$5,035	$5,167	$4,570	$5,925
TOTAL	$3,710	$30,099	$24,357	$22,035	$42,979

Outcome/Cost	Standard Care	RYGB	VSG	LAGB	BPD/DS
BMI 30-34.9					
Clinical Outcome					
BMI loss (mean)	1.17	8.45	7.93	6.305	10.14
Death (%)	1%	1%	1%	2%	2%
Reoperation (%)	0%	6%	3%	12%	7%
Medical complication (%)	0%	11%	13%	2%	21%
Diabetes resolution (%)	1%	10%	10%	9%	13%
Hypertension resolution (%)	3%	16%	20%	15%	16%
Hyperlipidemia resolution (%)	4%	22%	17%	8%	22%
Costs ($)					
Procedure	$3,042	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$787	$402	$1,478	$893
Other Complications	$0	$4,274	$4,406	$3,809	$5,164
TOTAL	$3,042	$29,338	$23,596	$21,274	$42,218
BMI 35-39.9					
Clinical Outcome					
BMI loss (mean)	1.35	9.75	9.15	7.275	11.7
Death (%)	1%	2%	2%	2%	2%
Reoperation (%)	0%	6%	3%	12%	7%
Medical complication (%)	0%	11%	13%	2%	21%
Diabetes resolution (%)	2%	15%	15%	14%	20%
Hypertension resolution (%)	4%	20%	25%	18%	20%
Hyperlipidemia resolution (%)	4%	23%	18%	9%	23%
Costs ($)					
Procedure	$3,500	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$787	$402	$1,478	$893

Outcome/Cost	Standard Care	RYGB	VSG	LAGB	BPD/DS
Other Complications	$0	$4,845	$4,977	$4,380	$5,735
TOTAL	$3,500	$29,909	$24,167	$21,845	$42,789
BMI≥40					
Clinical Outcome					
BMI loss (mean)	1.62	11.7	10.98	8.73	14.04
Death (%)	1%	2%	2%	2%	3%
Reoperation (%)	0%	6%	3%	12%	7%
Medical complication (%)	0%	11%	13%	2%	21%
Diabetes resolution (%)	3%	23%	23%	21%	29%
Hypertension resolution (%)	5%	24%	30%	22%	24%
Hyperlipidemia resolution (%)	4%	23%	17%	9%	23%
Costs ($)					
Procedure	$4,269	$24,277	$18,788	$15,987	$36,160
Reoperation	$0	$787	$402	$1,478	$893
Other Complications	$0	$5,820	$5,952	$5,356	$6,711
TOTAL	$4,269	$30,884	$25,142	$22,820	$43,764

BPD = biliopancreatic diversion; ICER = incremental cost-effectiveness ratio; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; VSG = vertical sleeve gastrectomy.

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

Reference Case Analysis – Bariatric Surgery Versus Standard Care (10-year Time Frame)

In the 10 year time horizon analysis, bariatric surgery resulted in additional quality-adjusted life-years (QALYs) and increased costs compared with standard care (see **Table 9** 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 off $37,423 for RYGB. VSG and LAGB are less costly, but less effective than RYGB, while BPD/DS is more expensive and more effective. However, in comparison to standard care, cost-effectiveness estimates are similar for all surgery types (ranging from $29,000 - $47,000 per QALY gained). Cost-effectiveness ratios were not calculated for VSG and LAGB in reference to RYGB (because they were less effective). The cost per QALY gained for BPD/DS was $77,574 in comparison to RYGB across all levels of BMI.

In keeping with clinical results at one year of follow-up, cost-effectiveness values were most favorable in patients with a BMI of 40 or above. 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 more pronounced 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).

Table 9: 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	NA	NA
RYGB	$54,110	8.0807	$37,423	NA
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	NA	NA
RYGB	$49,735	8.3529	$53,021	NA
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	NA	NA
RYGB	$52,886	8.1351	$42,534	NA
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	NA	NA
RYGB	$58,257	7.8630	$30,995	NA
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

BPD = biliopancreatic diversion; ICER = incremental cost-effectiveness ratio; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; VSG = vertical sleeve gastrectomy.

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

Sensitivity analyses — bariatric surgery versus standard care

We performed a series of one-way sensitivity analysis 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 12** on the following page. The ICERs range from $5,444/QALY to $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 (see Appendix E). Similarly, as the time horizon of the analysis is reduced, the incremental cost per QALY gains for bariatric surgery increase (see Appendix E).

The model was also sensitive to cost of bariatric surgery. In the base case, we assumed that RYGB costs $24,277. However, we ran analyses where the cost of RYGB was varied by 50 to 200%. The ICER ranged from $10,009 to $72,968, respectively.

We also investigated a best case scenario where we assume that the BMI reduction observed in year 1 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 ranged 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 varied the mean BMI. The ICER ranged from $30,995/QALY to $53,021/QALY when the BMI was varied from 45 to 32.5 (i.e., better results at higher BMI). The results were largely unchanged when other model inputs such as discount rate, increase in costs by incremental were considered (see Appendix E).

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

Figure 12: Tornado diagram of bariatric surgery (RYGB) vs. standard care using 10 year time horizon
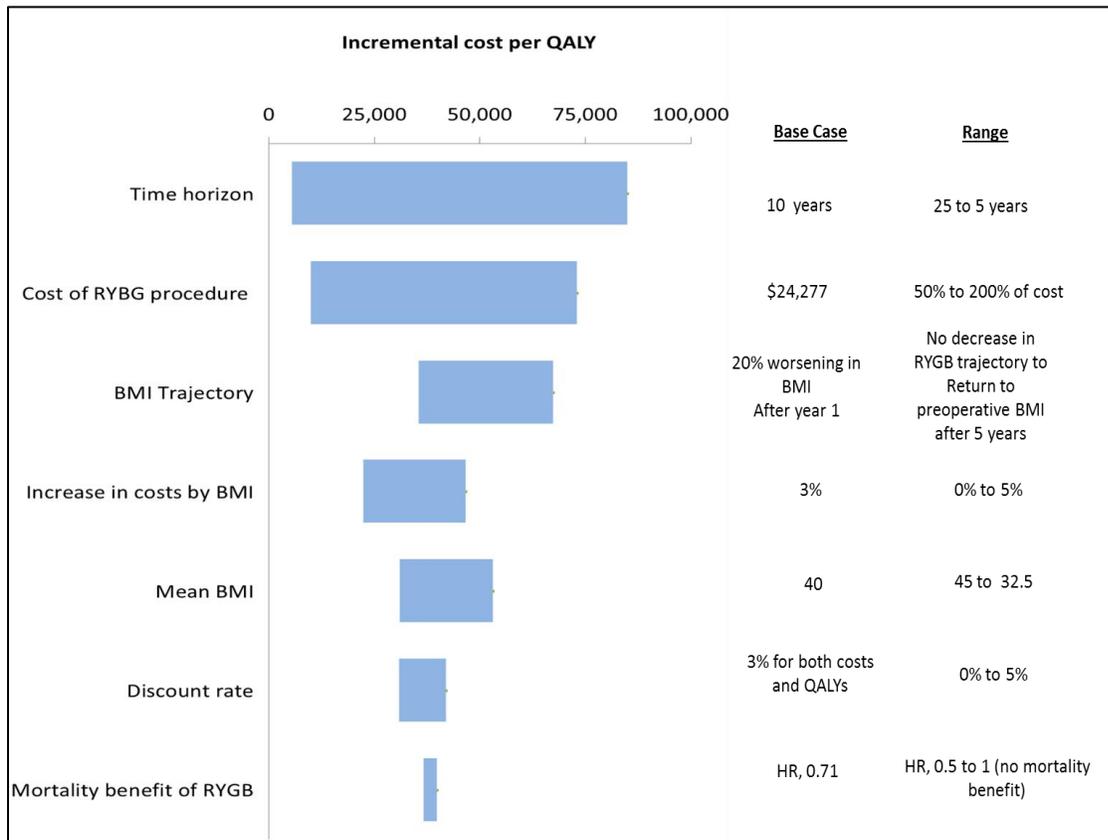
Discussion

We compared the cost-effectiveness of four bariatric surgery procedures to standard nonsurgical 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). Across all levels of BMI and procedure type, we found that surgical procedures to treat obesity improve health related quality of life, reduce BMI and other comorbidities, and are associated with higher healthcare costs compared to standard nonsurgical management. Cost-effectiveness estimates for bariatric surgery ranged from $23,784 to $63,011, suggesting that bariatric surgery for the treatment of obesity may be considered cost-effective in comparison to well-accepted benchmarks (i.e., $50,000-$100,000 per QALY gained). These findings were robust to a range of sensitivity analyses, including those involving no reduction in all-cause mortality with bariatric surgery and complete weight regain after five years following surgery.

We found more favorable cost-effectiveness estimates for bariatric surgery among patients with higher BMI (i.e., BMI ≥40) compared to those with lower BMI levels. This finding was largely attributable to larger absolute and relative reductions in BMI observed among patients with higher BMI, which in turn affected survival, cost, and QALY estimates favorably in the decision model. We also found that cost-effectiveness estimates were largely influenced by choice of time horizon. To enhance transparency, we applied a time horizon of 10 years for the primary analysis but also considered other time horizons. Findings for bariatric surgery were more favorable (< $10K per QALY) compared to standard nonsurgical

management in our analysis employing a longer time horizon of 25 years. Other studies have reported similar findings related to time horizon (Padwal, 2011).

The results of this cost-effectiveness analysis were less clear for choice among the various bariatric surgical procedures. All of the procedures considered in our analysis were associated with cost-effectiveness estimates that may be considered attractive compared with standard care. However, available data on differences between treatments in head-to-head evaluations translated into relatively small differences in QALY gains over the time horizons of interest in our evaluation (i.e., ~3 months of quality-adjusted survival over 10 years of follow-up between the most and least effective procedures). Nevertheless, these procedures do differ in terms of cost and complication rates, all of which are presented for review.

Our findings aligned closely with those reported in other economic evaluations (Padwal, 2011; Wang, 2014). Padwal and colleagues conducted a systematic review of health economic evaluations and identified 13 studies, all of which reported that bariatric procedures were cost-effective at willingness-to-pay thresholds <$50,000 per QALY gained over time horizons ranging from two years to lifetime (Padwal, 2011). Similar to our study, more favorable findings were reported among health economic evaluations which applied longer time horizons and/or considered patients with more severe obesity (i.e., BMI≥40) (Padwal, 2011; Wang, 2014).

Despite the favorable results of our study, there remain notable limitations. First, there were considerable gaps in available clinical evidence, and the cost-effectiveness of these procedures is highly dependent upon assumptions related to initial BMI loss and forecasted change in BMI over the time horizon. To address this limitation, we employed several BMI trajectory scenarios and found that results were robust under several assumptions. Further, there was considerable variation in patient populations, study design, and other features across studies, which limits the comparability of clinical evidence among bariatric surgery procedures. As a result, we were forced to make assumptions around the comparative clinical effects in the model. Rigorous, long-term studies are needed to better characterize the cost-effectiveness of the different bariatric procedures, particularly in relation to durability of weight loss and comorbidity remission over the long term.

9. Recommendations for Future Research

When the Health Care Authority commissioned their initial review of bariatric surgery for the pediatric population in 2007, no suitable comparison studies were identified. While the evidence base was larger for surgical procedures in adults, the availability of randomized or observational comparisons was still quite sparse. This was problematic on many levels, but the foremost challenge was what level of incremental benefit to ascribe to bariatric surgery given the lack of rigorous, controlled data.

Much has changed in the last several years, and there are now studies comparing bariatric procedures to nonsurgical control interventions as well as head-to-head comparisons of the major procedures to each other. There are even a handful of comparison studies conducted specifically in adolescents and children.

That said, the available studies still suffer from major structural and analytic flaws that challenge their interpretability and applicability. Below we list major design considerations for future research studies that should further improve the evidence base for bariatric surgery.

1. Utilization of Techniques of Survival Analysis

Obesity is a physically and mentally complex condition, and affects both the medical challenges of caring for the patient as well as the patient's ability to maintain the right lifestyle for preserving the potential benefits over the long term. Long-term studies of bariatric procedures are few and far between, and those that do exist suffer from significant loss to follow-up in large part because of the difficulty in maintaining patients in post-surgical programs. However, the true long-term benefits of surgery will not be known until definitive evidence on long-term weight reduction, weight regain and comorbidity relapse, and long-term harms are better measured. Most of the available studies examine these outcomes 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 timepoints discard the information provided by patients who were lost to follow-up between the timepoints of interest. To address this, future long-term studies should use techniques of survival analysis to assess the likelihood of long-term success as well as the risks of relapse, using multivariate techniques such as Cox proportional hazards models to control for differences between groups and to evaluate outcomes at multiple timepoints.

2. Standardized Measurement

It is also the case that comparisons of key outcomes of interest such as surgical complications and comorbidity remissions are made problematic by a lack of standardized definitions of these outcomes. For example, diabetes remission may be based solely on laboratory findings in some studies but also include cessation of medications in others. Some studies use existing methods to assess severity of surgical complications (e.g., Clavien system) while others rely on the interpretation of the investigators to gauge severity. Given the number of clinical guidelines promulgated by multiple clinical societies, it would seem prudent for these major societies to develop consensus statements on how best to measure these critical outcomes, so that the results of future studies can more easily be compared.

3. Collection of Data on Clinical Sequelae of Comorbidities

As noted in this review, data are accumulating on resolution of key comorbidities after bariatric surgery, including type 2 diabetes, hypertension, hyperlipidemia, and sleep apnea. Resolution has been defined based on laboratory parameters and receipt of medication, however, and has not been extended to

consider the important sequelae of these comorbidities. For example, many patients undergoing bariatric surgery have had longstanding type 2 diabetes, so tracking rates of key microvascular (e.g., retinopathy) and macrovascular (e.g., myocardial infarction) events even over shorter-term follow-up periods would be prudent. In addition, reductions in the rates of key clinical events over longer-term follow-up is likely to be considered a better measure of the durability of bariatric surgery's benefits than shorter-term improvement in comorbidity levels.

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