

Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Bariatric Surgery and Non-Surgical Therapy in Adults with Metabolic Conditions and Body Mass Index of 30 to 34.9

I. Background and Objectives for the Systematic Review

Bariatric surgery, also known as weight loss surgery, is a group of surgical procedures usually performed on people who are morbidly obese (either with BMI > 40 or BMI \geq 35 with comorbidities such as diabetes), for the purpose of losing weight and preventing future comorbidity. Types of bariatric surgery include laparoscopic adjustable gastric banding (LAGB), which reduces the size of the stomach with an implanted medical device; Roux-en-y gastric bypass (RYGB), which re-routes the small intestine to a small stomach pouch; biliopancreatic diversion with duodenal switch (BPD/DS), which redirects the pancreatic/biliary content flow and constructs a small stomach tube; and sleeve gastrectomy, which removes a portion of the stomach leaving a narrowed portion in continuity.

Studies show that these procedures cause significant loss of weight. In addition, bariatric surgery such as LAGB and RYGB have been found to be far more effective than conventional non-surgical therapy at improving diabetes in the short term, especially in the morbidly obese population.¹⁻⁴ While both techniques are now routinely performed laparoscopically, and they have demonstrated reduced obesity-related morbidity and mortality, malabsorptive procedures (e.g., RYGB) appear to be superior over restrictive procedures (e.g., LAGB) for obtaining weight loss and improvement in diabetes-related outcomes in morbidly obese patients.⁵ A literature scan also suggests that LAGB is a less complex procedure as compared to RYGB and it produces weight loss, but may not have as large an effect on diabetes as other bariatric procedures.^{6,7}

It has been postulated that the surgical stapling and exclusion of a portion of the stomach involved in both RYGB and the gastric sleeve may alter neuropeptide levels that play a role in metabolism. However, bariatric surgery is costly, and as with any surgical procedure, bariatric surgery may be associated with various adverse effects. Furthermore, there have been reports that as many as 1/3 of laparoscopic band patients, 3-5 years out, are not able to maintain weight loss due to patient compliance and other issues.⁸ Adjustable laparoscopic gastric banding is associated with a number of complications, resulting in removal rates as high as 20-30%.^{9,10} Some patients are even converted to a RYGB. The benefits/risks ratio in the long term is also a concern: effectiveness and safety data are very limited to support any long-term benefits/risks claims.

National Institutes of Health (NIH) guidelines from 1991 established the following criteria for patients considering bariatric surgery: individuals with Body Mass Index (BMI) > 40 kg/m² or BMI \geq 35 kg/m² with significant co-morbidities (following physician

supervised attempts at weight loss).¹¹ The Center for Medicare & Medicaid Services (CMS) has also made a decision to cover bariatric surgery for treatment of co-morbidities associated with morbid obesity (BMI \geq 35) for a variety of procedure types.¹² However, some preliminary studies have shown that patients whose BMI fall below these criteria may also experience similar weight loss and its associated benefits.¹³ Despite the potential harms associated with bariatric surgery, there seems to be an increase in pressure for the coverage of bariatric surgery such as LAGB for metabolic conditions (e.g., type 2 diabetes), even in settings where its use is not fully supported. Several experts have suggested that the minimum BMI requirement for patients with type 2 diabetes undergoing bariatric surgery be lowered (e.g., less than 35 kg/m²). However, CMS has recently decided that it will not cover bariatric surgery for beneficiaries who have type 2 DM and a BMI < 35, specifically for open and laparoscopic Roux-en-Y gastric bypass (RYGBP), LAGB, and open and laparoscopic biliopancreatic diversion with duodenal switch (BPD/DS).¹⁴

Given the uncertainties pertaining to the bariatric surgical procedures (the minimum BMI requirement, comparative effectiveness especially in the long term, potential adverse effects, etc.), a review of the relative benefits and harms of the alternative approaches to treatment of metabolic conditions such as diabetes (e.g., LAGB, RYGB, and other new procedures) and traditional medical management is needed in the patient population with BMI below 35. This review should help 1) better understand long-term benefits and harms associated with different treatment approaches; 2) clarify the types of studies that should be done to determine/establish long-term patient benefits; and 3) develop guideline revisions. In the event that data are lacking, an assessment should be made of what are the key variables influencing the long-term net benefits compared to harms, to inform the design of future research studies. This could include complications post-surgery, elective removal of the band, and maintenance.

II. The Key Questions

KQ1: What does the evidence show regarding the comparative effectiveness of bariatric surgery for treating adult patients with BMI of 30 to 34.9 and metabolic conditions, including diabetes? Are certain surgical procedures more effective than others (laparoscopic adjustable gastric banding, gastric bypass, or sleeve gastrectomy)?

Population(s):

Adults (age 18+) with BMI of 30 to 34.9 and metabolic conditions such as diabetes.

Interventions:

Bariatric surgery:, LAGB, RYGB, BPD/DS, and sleeve gastrectomy, and associated devices approved by the U.S. FDA. A list of different devices, their manufacturers, and FDA approved indications is present in Appendix A.

Comparators:

This key question will conduct within group comparison – comparators will be



alternative surgical procedures including LAGB, RYGB, BPD/DS, and sleeve gastrectomy.

Outcomes:

- Primary outcomes:
 - Short-term:
 - fasting glucose level
 - hemoglobin A1c (HbA1c)
 - triglycerides
 - blood pressure
 - Long-term:
 - % with sleep apnea
 - % with GERD
 - % with diabetes resolution/improvement
 - % off anti-diabetic medications
 - % being euglycemic
 - time to diabetes resolution
 - weight loss outcomes (change in BMI, % excess weight loss).
- Secondary outcomes:
 - healthcare utilization/economics
 - quality of life measures
- Adverse events:
 - Short-term:
 - mortality
 - Long-term:
 - mortality
 - reoperation after bariatric surgery (i.e. band removal, band-to-RYGB conversion)
 - gastric surgery adverse events: bowel obstruction, incisional hernia
 - RYGB-specific adverse events: anastomosis complications (i.e. staple-line disruption or ulcer), nutritional deficiencies
 - LAGB-specific adverse events: band and complications (i.e. slippage or leakage), port/tubing complications, gastric complications (i.e. pouch dilatation or erosion)

Timing:

No minimum duration of follow-up for surgical studies.

Short-term outcomes: 1 year or best available post surgery intervention.

Long-term outcomes: 5 years or best available post surgery intervention.

Settings:

Any setting in which bariatric surgery takes place.

KQ2: What does the evidence show regarding the comparative effectiveness of bariatric surgery versus conventional non-surgical therapies for treating adult patients with BMI of 30 to 34.9 and metabolic conditions?

Population(s):

Same as in KQ1.

Interventions:

Same as in KQ1.

Comparators:

This key question will conduct cross group comparison – comparators will be conventional non-surgical therapies (diet, exercise, pharmaceuticals). A list of different FDA-approved pharmacologic agents, their manufacturers, and FDA approved indications is present in Appendix B.

Outcomes:

All outcomes for surgical procedures are the same as in KQ1.

Outcomes for non-surgical therapies include:

- Primary outcomes: Same as in KQ1.
- Secondary outcomes: Same as in KQ1.
- Adverse events:
 - Short-term:
 - mortality
 - systemic medical complications (i.e. myocardial infarction, stroke)
 - Long-term:
 - mortality
 - adverse effects of medications

Timing:

Minimum duration of follow-up: Same as in KQ1.

Short-term outcomes: 1 year or best available post surgery or medical intervention.

Long-term outcomes: 5 years or best available post surgery or medical intervention.

Settings:

Any setting in which bariatric surgery or other weight loss programs take place.

KQ3: What are the potential short term adverse effects and/or complications involved with bariatric surgery for treating adult patients with BMI of 30 to 34.9 who have metabolic conditions?

Population(s):

Same as in KQ1.

Interventions:

Same as in KQ1.

Comparators:

N/A

Outcomes:

Short-term adverse events:

- mortality
- other

Timing:

1 year or best available post surgery intervention.

Settings:

Same as in KQ1.

KQ4: Does the evidence show racial and demographic disparities with regard to potential benefits and harms associated with bariatric surgery for treating adult patients with BMI of 30 to 34.9 and metabolic conditions? What other patient factors (social support, counseling, pre-operative weight loss, compliance) are related to successful outcomes?

Population(s):

Demographic subsets of the populations described in KQ1. Demographic subsets include different racial/ethnic groups, different age groups, and different genders.

Interventions:

Same as in KQ1.

Comparators:

N/A

Outcomes:

Efficacy and effectiveness outcomes are the same as in KQ1. Outcome measures for harms, or adverse events, are the same as in KQ3, and KQ5 below.

Timing:

Same as in KQ1.

Settings:

Same as in KQ1.

KQ5: What does the evidence show regarding long-term benefits and harms of bariatric surgery for treating adult patients with BMI of 30 to 34.9 and who have metabolic conditions? How do they compare to short-term outcomes (within 1 year from surgery)?

Population(s):

Same as in KQ1.

Interventions:

Same as in KQ1.

Comparators:

N/A. This key question will compare long-term and short-term outcomes (benefits and harms) of surgical procedures.

Outcomes:

Same as in KQ1.

Timing:

Same as in KQ1.

Settings:

Same as in KQ1.

III. Analytic Framework

Figure 1 presents the analytic framework for this Comparative Effectiveness Review, with the five key questions depicted within the context described in the previous sections.

First, by using data from clinical trials and large cohort studies, evidence of benefits and harms of different types of bariatric surgeries and conventional non-surgical therapies in treating targeted patients (those with metabolic conditions and BMI of 30 to 34.9) will be documented. Both short- and long-term outcomes are included. Two sets of effectiveness comparisons will be conducted: 1) within group comparison: compare alternative surgical approaches (LAGB, RYGB, sleeve gastrectomy, etc.). Results of this comparison will answer the first key question; 2) cross group comparison: compare surgical procedures to conventional non-surgical therapies (diet, exercise, pharmaceuticals, etc.). Results of this comparison will answer the second key question.

Documented short- and long-term benefits and harms of surgical procedures will be compared too; the results will answer key question three and five.

Benefits and harms for specific subpopulations (by gender, age, and race/ethnicity) and other patient factors (social support, counseling, pre-operative weight loss, compliance) will be examined and summarized. This will answer key question four.

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included that address the populations, interventions, comparators, and outcomes described above. The following study design types will be included: case series, cohort, case control, controlled trial, and other designs. Minimum sample size of the study is two (i.e., individual case report will not be reviewed). Non-English language studies, as long as they meet the inclusion criteria and a proper translator can be

identified, will be included in the review. Relevant grey literature will be included. We will not limit the publication date of studies. If considered necessary, study authors will be contacted for additional data.

The following studies will be excluded: 1) studies that did not report any outcomes of efficacy, effectiveness, or safety/adverse events; 2) non-surgical studies with less than 1 year follow-up; 3) background articles; and 4) single case reports.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

A librarian has performed the initial literature search. Two trained reviewers – a psychiatrist and a health researcher – will scan the titles/abstracts of the list run by the librarian and select studies for full-text screen. For each of the selected study, reviewers will perform further reference mining by scanning titles listed in the reference section to identify additional articles to be included. Reviewers will reconcile their selections and make joint decisions, following all the inclusive/exclusive criteria listed in previous sections.

Based on discussions among team members (project leader, surgeon, librarian, etc.), the following databases are identified to possibly include relevant studies of interest and thus are selected to perform the initial literature search.

Databases

- DARE (Database of Abstracts of Reviews of Effects)
- Cochrane library of systematic reviews
- CENTRAL (Cochrane Central Register of Controlled Trials)
- PubMed (National Library of Medicine, includes MEDLINE)
- EMBASE (Biomedical and pharmacological bibliographic database)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Other sources

- Clinicaltrials.gov
- References of included studies
- References of relevant reviews
- Personal files from related topic projects

Our literature search will focus on identifying controlled trials and large observation studies. Other sources of literature include comments from public and peer reviews and recommendations from our Technical Expert Panel. All the information we gather will be discussed in weekly project meetings in a timely manner. Revisions of search terms and strategies will be updated according to the decisions made at the meetings. Additional studies will be included if they meet the inclusion criteria illustrated above; in rare case when the inclusion/exclusion criteria need to be modified, AHRQ and Technical Expert Panel will be consulted.

C. Data Abstraction and Data Management

Data will be independently abstracted by two researchers trained in the critical assessment of evidence. The following data will be abstracted from included studies: trial name (if applicable), setting, population characteristics (including sex, age, ethnicity, and diagnosis), eligibility and exclusion criteria, interventions (including dose for medications, frequency for exercise programs, and duration), any co-interventions,

other allowed medication, comparisons, and results for each outcome. Intent-to-treat results will be recorded if available.

For efficacy/effectiveness outcomes, a statistician will extract data. A surgeon will choose which outcomes are most appropriate to pool for the surgery studies, while a physician weight loss expert will choose for the non-surgical studies. Poolability across studies is also important; the physicians, the statistician, and the project team will jointly make the selection based on their professional knowledge and also considering the frequency of an outcome measure being reported by the trials. A minimum of three studies is required for meta-analysis. For each intervention within a trial, the sample size, mean outcome, and standard deviation will be extracted. If a study does not report a follow-up mean or if a follow-up mean can not be calculated from the given data, the study will be excluded from analysis. For those trials that do not report a follow-up standard deviation, we will impute one by assigning the average standard deviation from other trials that report the standard deviation for the same outcome. If fewer than two trials are available with standard deviations, then we will impute the follow-up standard deviation by taking one-fourth the theoretical range of the scale.

D. Assessment of Methodological Quality of Individual Studies

To assess internal validity of controlled trials, we will abstract data on the adequacy of the randomization method; the adequacy of allocation concealment; maintenance of blinding; similarity of compared groups at baseline and the author's explanation of the effect of any between-group differences in important confounders or prognostic characteristics; specification of eligibility criteria; maintenance of comparable groups (i.e., reporting of dropouts, attrition, crossover, adherence, and contamination); the overall proportion of subjects lost to follow-up and important differences between treatments; use of intent-to-treat analysis; post-randomization exclusions, and source of funding. We will define loss to follow-up as the number of patients excluded from efficacy analyses, expressed as a proportion of the number of patients randomized.

To assess external validity, we will record the number screened, eligible, and enrolled; the use of run-in and washout periods or highly selective criteria; the use of standard care in the control group; and overall relevance. Funding source will be also abstracted.

To arrive at a quantitative measure for controlled trials, we will use the Jadad scale, which was developed for drug trials. This method measures quality on a scale that ranges from 0-5, assigning points for randomization, blinding, and accounting for withdrawals and dropouts. (Across a broad array of meta-analyses, an evaluation found that trials scoring 0-2 report exaggerated results compared with trials scoring 3-5. The latter have been called "good" quality and the former called "poor" quality.)

For any disagreement that may arise regarding the quality assessment, issues will be brought to the project meeting and group decisions will be made by the research team.

E. Data Synthesis

Our a priori analytic plan is to summarize the evidence for efficacy and effectiveness for surgical procedures (LAGB, RYGB, sleeve gastrectomy, etc.), firstly comparing within surgical procedures, and then comparing surgical procedures with conventional non-surgical therapies. The evidence of risks (adverse events) will be summarized for each surgical procedure and non-surgical therapy.

For the efficacy and comparative effectiveness analyses, we will focus on studies that report outcomes 1) without a minimum length for surgical procedures, and 2) with at least one year follow-up for non-surgical therapies. Effect sizes will be calculated for each comparison. If all studies within a subgroup use the same scale, then the effect size does not need to be standardized and a mean difference will be calculated. For subgroups where pooling is done across several scales, we will calculate an unbiased estimate using the Hedges' *g* effect size. Since most of the scales used as outcome measures in the pooled analyses are scored so that more severely symptomatic persons have higher scores, a negative effect size indicates that the surgical procedure has a higher efficacy than does the non-surgical therapy.

For trials that are judged sufficiently clinically similar to warrant meta-analysis, we will estimate a pooled random-effects estimate of the overall mean difference in outcome measure. The individual trial mean differences are weighted by both within-study variation and between-study variation in this synthesis.

We will also assess publication bias. Tests will be conducted using the Begg adjusted rank correlation test and the Egger regression asymmetry test.

All meta-analyses will be conducted with Stata statistical software, version 8.2 (Stata Corp., College Station, Texas).

For groups of trials not judged sufficiently clinically similar to support meta-analysis, we will perform a narrative synthesis. Major outcomes and findings of the studies will be further presented in tables to compare different interventions.

In both meta-analysis and narrative descriptions, diabetes related outcomes (e.g., blood glucose) will be the most important outcomes to report. We will also seek inputs from key informants and Technical Expert Panel by holding conference calls to prioritize relevant outcomes.

F. Grading the Evidence for Each Key Question

We will assess the overall strength of evidence for intervention effectiveness using guidance suggested by the U.S. Agency for Healthcare Research and Quality

(AHRQ) for its Effective Healthcare Program. This method is based loosely on one developed by the Grade Working Group, and classifies the grade of evidence according to the following criteria:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence on the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

The evidence grade is based on four primary domains (required) and four optional domains. The required domains are risk of bias, consistency, directness, and precision; the additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias. For this review, we will use both this explicit scoring scheme and the global implicit judgment about “confidence” in the result. Where the two disagree, we will go with the lower classification.

V. References

1. Shekelle PG, Morton SC, Maglione MA et al. (2004) Pharmacological and Surgical Treatment of Obesity. Evidence Report/Technology Assessment No. 103. AHRQ Publication No. 04-E028-2. Rockville, MD: Agency for Healthcare Research and Quality.
2. Medpage Today Article – ASMBS: Bariatric Surgery Found Superior to Drugs in Controlling Diabetes
<http://www.medpagetoday.com/Endocrinology/Diabetes/9866>
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4. Dixon JB, O'Brien PE, Playfair J et al. (2008) Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA*. 299:316-323.
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7. Bowne WB, Julliard K, Castro AE, Shah P, Morgenthal CB, Ferzli GS. Laparoscopic gastric bypass is superior to adjustable gastric band in super morbidly obese patients: A prospective, comparative analysis. *Arch Surg.* 2006 Jul;141(7):683-9.
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12. CMS National Coverage Decision for Bariatric Surgery for Treatment of Comorbidities Associated with Morbid Obesity, 2006
13. Choi J, DiGiorgi M, Milone L et al. (2009). Outcomes of laparoscopic adjustable gastric banding in low BMI patients. *Surgery for Obesity and Related Diseases*, 5(3): S5-S5.
14. Centers for Medicare & Medicaid Services. Decision Memo for Surgery for Diabetes (CAG-00497N), February 12, 2009 [Cited September 23, 2010]. Available from:
<http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?from2=viewdecisionmemo.asp&id=219&>

VI. Definition of Terms

1. Bariatric surgery: Surgery on the stomach and/or intestines to help a person with severe obesity lose weight.
2. Body Mass Index (BMI): A person's weight in kilograms divided by their height in meters squared, used to define normal weight, overweight, and obesity.
3. Gastric bypass: A surgical weight-loss procedure that involves the creation of a small stomach pouch to restrict food intake and construction of bypasses of the

duodenum and other segments of the small intestine to cause malabsorption (decreased ability to absorb nutrients from food).

4. Gastroesophageal Reflux Disease (GERD): A condition commonly referred to as acid reflux, in which the liquid content of the stomach regurgitates (backs up or refluxes) into the esophagus.
5. Laparoscopic adjustable band: A surgical weight-loss procedure that involves the placement of an adjustable belt around the upper portion of the stomach, restricting the size of the stomach and the amount of food it can hold.
6. Metabolic condition: A constellation of syndromes including impaired fasting glucose (prediabetes) and diabetes mellitus that increase the risk of cardiovascular disease.
7. Sleep apnea: A disorder characterized by a reduction or pause of breathing (airflow) during sleep.
8. Sleeve gastrectomy: A surgical weight-loss procedure in which the stomach is reduced to about 15% of its original size, by surgical removal of a large portion of the stomach.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Appendix A: List of bariatric surgery devices, manufacturers, and FDA approved indications

Device	Manufacturer	FDA Approved Indication(s)
Lap-Band	Allergan Inc	Weight reduction for severely obese patients with a body mass index (BMI) of at least 40 or a BMI of at least 35 with one or more severe comorbid conditions, or those who are 100lbs. or more over their estimated ideal weight. Only for severely obese adult patients who have failed more conservative weight-reduction alternatives, such as supervised diet, exercise and behavior modification programs.
Realize (Swedish) Adjustable Gastric Band	Ethicon Endo-Surgery, Inc (part of Johnson & Johnson)	Weight reduction for morbidly obese patients with a body mass index (BMI) of at least 40 or a BMI of at least 35 with one or more severe comorbid conditions. Only for morbidly obese adult patients who have failed more conservative weight-reduction alternatives, such as supervised diet, exercise and behavior modification programs.
Midband	Médical Innovation Développement	Not approved. ^b
Heliogast band	Helioscopie	Not approved. ^b
A.M.I Soft Gastric Band	Austrian Agency for Medical Innovations Ltd	Not approved. ^b
BIORING	Cousin Biotech	Not approved. ^b

^a Only FDA-approved devices will be included in the review.

^b Device is not available in the United States, if used in a research study the study will be excluded from the review.

Appendix B: List of pharmacologic agents, generic (name brand), manufacturers, and FDA approved indications

Pharmacologic Class	Generic (Name brand)	Manufacturer	FDA Approved Indication(s) ^a
GLP-1 receptor agonist	Liraglutide (Victoza)	Novo Nordisk	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Incretin Mimetic	Exenatide (Byetta)	Amylin Pharmaceuticals, Eli Lilly and Company	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
DPP-4 inhibitor	Sitagliptin (Januvia) Vildagliptin (Galvus)	Merck & Co Novartis	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Lipase inhibitor	Orlistat (Xenical, Alli)	Hoffmann La Roche Glaxosmithkline Cons	Obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet; to reduce the risk for weight regain after prior weight loss; indicated for obese patients with initial body mass index (BMI) $\geq 30 \text{ kg/m}^2$ or $\geq 27 \text{ kg/m}^2$ in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia). Weight loss in overweight adults, 18 years and older, when used along with a reduced-calorie and low-fat diet.
Norepinephrine, serotonin and dopamine reuptake inhibitor	Sibutramine (Meridia)	Abbott	Management of obesity including weight loss and maintenance of weight loss in conjunction with a reduced calorie diet; recommended for obese patients with initial body mass index $\geq 30 \text{ kg/m}^2$, or $\geq 27 \text{ kg/m}^2$ in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension).
Sympathomimetic amine	Diethylpropion (Tenuate)	Watson Pharms, Corepharma	Management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction in patients with an initial body mass index (BMI) of 30 kg/m^2 or higher and who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone.

^a Only FDA-approved pharmacologic agents will be included in the review.

Figure 1. Provisional analytic framework for evaluating the effectiveness and safety of alternative approaches to treatment of metabolic conditions in the patient population with BMI of 30 to 34.9

