

Evidence-based Practice Center Systematic Review Protocol

Project Title: Management and Outcomes of Binge Eating Disorder (BED)

I. Background and Objectives for the Systematic Review

Binge eating disorder (BED) is characterized by recurrent episodes of binge eating and, subsequently, significant psychological distress (e.g., shame, guilt). Recently recognized by the American Psychiatric Association (APA) as a distinct eating disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),¹ BED is considered a significant public health problem independently and for its impact on obesity and diabetes.^{2,3} The related problem, loss-of-control (LOC) eating, describes recurrent binge-like eating behavior in individuals who cannot meet full criteria for BED such as post-bariatric surgery patients and children. LOC eating has detrimental psychological and physical health effects,⁴⁻⁶ including significant distress and symptoms of depression,⁷ as well as excess weight gain in children and suboptimal weight loss and weight regain in post-bariatric patients. Table 1 lists the diagnostic criteria for BED (as defined in the current DSM-5 and earlier, in the DSM, Fourth Edition [DSM-IV]) and frequently-used definitions of LOC eating.

Table 1. Diagnostic Criteria for Binge Eating Disorder and Loss-of-Control Eating

Disorder or behavior	Criteria
DSM-IV and DSM-5 Criteria for Binge Eating Disorder (BED)	<ol style="list-style-type: none"> 1. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: <ol style="list-style-type: none"> a. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances b. The sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating) 2. Binge-eating episodes are associated with three (or more) of the following: <ol style="list-style-type: none"> a. Eating much more rapidly than normal b. Eating until feeling uncomfortably full c. Eating large amounts of food when not feeling physically hungry d. Eating alone because of being embarrassed by how much one is eating e. Feeling disgusted with oneself, depressed, or very guilty after overeating 3. Marked distress regarding binge eating is present 4. The binge eating occurs, on average, <ol style="list-style-type: none"> a. at least 2 days a week for 6 months (DSM-IV frequency and duration criteria) b. at least 1 day a week for 3 months (DSM-5 frequency and duration criteria) 5. The binge eating is not associated with the regular use of inappropriate compensatory behavior (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of anorexia nervosa or bulimia nervosa <p>DSM-IV does not include a BED severity grading scale.</p> <p>Applicable to DSM-5 only, BED severity is graded as follows:</p> <p>Mild: 1 to 3 episodes per week Moderate: 4 to 7 episodes per week Severe: 8 to 13 episodes per week Extreme: 14 or more episodes per week</p>

LOC Eating	<p>No standardized definition exists for LOC eating; however, parameters commonly used to describe and quantify LOC eating include the following:</p> <ol style="list-style-type: none"> 1. The presence of (an) objective binge-eating episode(s) (OBEs), whereby BED DSM criteria 1a and 1b above are met, <i>and/or</i> 2. The presence of (a) subjective binge-eating episode(s) (SBEs), whereby the amount of food consumed is not unambiguously large (as judged by the interviewer/assessor) but the patient views it as excessive and reports loss of control during such episodes; that is, BED DSM criterion 1b but not 1a is met, <i>and/or</i> 3. The presence of (a) subjective episode(s) of loss of control over eating among bariatric surgery patients, including engaging in eating behaviors that might be contraindicated after surgery.
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Abbreviations: DSM = Diagnostic and Statistical Manual of Mental Disorders; LOC = loss of control

Epidemiology of BED and LOC Eating

In the United States, the prevalence of BED among adults is ~ 3.5 percent in women and ~ 2 percent in men⁸ based on DSM-IV criteria and may be slightly higher based on DSM-5 criteria.^{9,10} BED is more common (as high as 30 percent) among obese individuals^{11,12,13} and has been found to be more prevalent among Hispanic populations than among any other groups defined by race or ethnicity.^{14,15} BED is typically first diagnosed in young adulthood (early to mid-20s) and symptoms often endure well beyond midlife,^{16,17} with the general course of illness sometimes including crossover to and from other eating disorders such as bulimia nervosa (BN) and anorexia nervosa (AN).^{9,18,19} The prevalence of LOC eating in post-bariatric surgery patients and in children is unknown, but may be as high as 25 percent in post-bariatric surgery patients^{20,21} and 32 percent in children at risk for adult obesity.⁶

Current Challenges Regarding the Diagnosis of BED and LOC Eating

In the diagnosis of BED, the assessment of a patient eating an “objectively large amount of food” is not wholly quantitative; rather, it requires the clinician’s evaluation of the patient’s self-report and is, therefore, at risk for detection bias. Neither DSM-IV nor DSM-5 established a minimal age for a diagnosis of BED, resulting in clinicians and researchers inconsistently describing behavior in adolescents and children. Some consider BED criteria in diagnosing adolescents and others consider LOC eating criteria. The term LOC eating is more consistently used when focusing on preadolescents or younger children. In the post-bariatric setting, the definition of LOC eating may extend beyond food amount to food types and patterns of intake that are contraindicated after surgery, and a critical question is whether LOC eating reflects presurgical eating pathology or *de novo* eating pathology subsequent to the surgery. Furthermore, a consistently endorsed definition of LOC eating does not exist; thus, the assessment of LOC eating may lack standardization across studies focusing on children and post-bariatric surgery patients.

Current Treatment Options for BED

Current treatments for BED and LOC eating include psychological and behavioral interventions, pharmacological interventions, complementary and alternative medicine (CAM) interventions, and combination approaches. To date, the psychological/behavioral approaches studied most frequently include cognitive behavioral therapy (CBT),²²⁻³¹

interpersonal psychotherapy (IPT),³²⁻³⁴ dialectical behavior therapy (DBT),³⁵⁻³⁷ and behavioral weight loss (BWL).

Pharmacological interventions include antidepressants (typically, selective serotonin reuptake inhibitors [SSRIs], but also norepinephrine reuptake inhibitors [NRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], and tricyclic antidepressants);³⁸⁻⁴⁸ anticonvulsants;^{49,50} gamma-aminobutyric acid (GABA) receptor agonists,^{51,52} and weight loss agents.^{53,54} Currently, however, none of these medications has a specific FDA-approved indication for BED.

There are relative advantages and disadvantages of currently available treatment options: pharmacological interventions may result in negative physical side effects. However, they are more easily accessible than psychological and behavioral interventions that require access to practitioners with specialized training in BED. Some studies⁵⁵ suggest the choice of the best treatment for a particular patient may be related to various patient characteristics, such as level of comorbid psychopathology and level of obesity.

Existing Guidelines Regarding the Treatment of BED

The APA,⁵⁶ the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom,⁵⁷ the Task Force on Eating Disorders of the World Federation of Societies of Biological Psychiatry,⁵⁸ and the American Dietetic Association (ADA; now the Academy of Nutrition and Dietetics)¹⁶ have issued treatment guidelines or recommendations for BED. Generally, there is strong support for the use of CBT and SSRIs; moderate support for IPT, DBT, topiramate, and imipramine. NICE guidelines indicate that medication monotherapy may be sufficient treatment for a subset of patients, and, across guidelines, there is agreement that the long-term effects of SSRIs are unknown. With a lower level of confidence, the APA also recommends zonisamide (an anticonvulsant medication), combination psychological and pharmacological approaches, non-weight-directed psychosocial approaches (i.e., “Health at Every Size”, mindful/intuitive eating, 12-step), and nutritional approaches consistent with the ADA’s endorsement of nutrition counseling by a registered dietitian to support health-centered behaviors rather than weight-centered dieting. Despite these similarities, there are some notable differences between organizations in their recommendations concerning how and when treatment is implemented. The APA recommends CBT incorporated into a team approach including psychiatrists, psychologists, dietitians, and social workers; the NICE guidelines recommend CBT-based self-help therapy followed, if necessary for non-responders, by CBT adapted specifically for BED then, if needed, alternatives such as IPT or DBT).

To improve the evidence base for treatment guidelines, further research is needed regarding the long-term efficacy of pharmacological interventions, efficacy of CAM treatments, treatment efficacy in diverse groups including ethnic minorities and children/adolescents, predictors of treatment response, harms and costs-benefit assessments of different treatments, treatment stepped-care models, and treatment efficacy in residential treatment settings, which have recently gained popularity in the U.S.

Current Challenges and Controversies Regarding the Treatment of BED

Many BED patients initially access treatment through a primary care physician who may be able to offer only a limited number of treatment options directly (usually just pharmacotherapy) or referral to psychologists, dietitians, and psychiatrists who also lack specific expertise in BED. It is largely unknown whether treatment protocols that are used in research studies and require clinically trained personnel with expertise in BED-specific interventions can be delivered effectively in more commonly available real-world settings. We will therefore carefully capture descriptions of treatment settings and separately highlight evidence from intervention studies implemented in more real world settings.

Commonly, along with achieving binge abstinence and reducing distress, weight reduction and improved metabolic health have been key outcomes in BED treatment studies and important treatment goals in clinical settings. Recently, however, some advocates, including the Health at Every Size (HAES) group (<http://www.haescommunity.org/resources.php>), have strongly endorsed removing weight-based outcomes in BED treatment while emphasizing greater body acceptance and intuitive eating. HAES maintains that weight-loss interventions are not only ineffective for treating BED but also detrimental because they contribute to the development and perpetuation of disordered eating behavior and psychopathology (binge eating, food and body preoccupation, yo-yo weight cycles, reduced self-esteem) as well as weight stigmatization and discrimination. Weight stigma awareness is also a central issue of another advocacy group, the Binge Eating Disorder Association (<http://bedaonline.com/binge-eating-disorder-blog/#.Up9vItIwldw>). In light of these stakeholder perspectives, we will not only collect data on traditional weight-related outcomes but also seek to capture information about more non-traditional non-weight-focused body image and eating behavior outcomes and interventions.

Impact on Clinical Decisionmaking or Policymaking

Patients enter treatment for BED with varying levels of concern about body shape and weight and varying amounts of health care coverage. These factors have a strong influence on choice of first-line treatment, the formulation of the comprehensive treatment plan and ultimately, treatment outcome. Individuals with BED seeking bariatric surgery can be denied coverage for their surgery even though an evidence base of poorer outcomes from surgery in patients with BED does not exist.⁵⁹ Recent federal legislation is making health insurance more accessible for previously uninsured or underinsured Americans and improving parity for mental health services, but the impact of these laws on access to treatment options for BED is yet to be determined. Children and adolescents with LOC eating are presenting for treatment and bariatric surgery in greater numbers, but no treatment guidelines are tailored to their circumstances. Also, increasingly, patients are entering treatment using over-the-counter products and dietary supplements with known or suspected effects on appetite, mood, and weight regulation; these scenarios pose additional challenges for providers evaluating treatment options. This report is intended to help inform future decision- and policymaking regarding treatment for BED and for LOC eating in bariatric surgery patients and in children. By doing so, it

can potentially inform future development of clinical best practice guidelines for these patients.

Rationale for Evidence Review

Previous systematic reviews have addressed psychological treatments for BN and BED (2009),⁶⁰ self-help and guided self-help for eating disorders (2006),⁶¹ and management of eating disorders, including BED (the AHRQ review, 2006).⁶² The 2006 AHRQ review of treatment for eating disorders was unable to draw definitive conclusions concerning the best treatment choices for BED because many of the available treatments had been evaluated in only single studies or too few studies of sufficient quality.⁶² Since that report, the literature on treatment of BED has expanded, the diagnostic criteria have changed, and a greater interest in BED and LOC eating in bariatric patients and children has emerged. These factors underscore the need for a new systematic review that captures the new information and presents it in a format that can bridge the old and new diagnostic criteria and improve understanding of BED and LOC eating across the lifespan as well as factors that influence their progression, maintenance, and resolution.

An updated review of RCTs, nonrandomized trials, and observational studies (combining results based on meta-analysis, when appropriate) is timely and needed to inform clinical decisionmaking. Knowing which factors might influence treatment (such as coexisting psychological and physical problems) should allow clinicians to modify or adapt a treatment plan according to an individual patient's needs or preferences, raising the potential to maximize treatment benefits and avoid treatment harms.

Including bariatric surgery patients as a separate population in the review is timely and needed. We can thus address pressing questions about the relevance of BED as a negative prognostic indicator for bariatric surgery, the extent to which nonsurgical interventions (e.g., psychotherapy) for BED may be beneficial in reducing or preventing LOC eating after surgery, and the appropriate timing of these nonsurgical interventions (before or after surgery). The focus on LOC eating in children is also timely as it will inform the larger public health issue of childhood obesity.

Lastly, novel interventions (such as mindful/intuitive eating, body acceptance-focused therapy, CAM approaches and novel pharmacological agents) have emerged as more common treatment options since the previous EPC systematic review, and they are not reflected in the evidence base reviewed for current treatment guidelines; therefore, their inclusion in this review will be an important contribution to the field.

In sum, this report will be a significant source of much-needed information and guidance for improving clinical decisionmaking by identifying treatment approaches for BED and LOC eating that are most strongly supported by the evidence base.

II. The Key Questions

As listed below, the review will address 15 Key Questions (KQs) that were posted for public comment. These KQs reflect input received from the public. Specifically, sexual orientation was added as a characteristic of interest in relation to course of illness in adult populations (KQs 5 and 10). It is unknown whether sexual orientation influences treatment seeking and, thus, course of illness. Sexual orientation may be relevant for

studies of adults with BED or LOC eating but less relevant for children with LOC given that sexual orientation is often not yet established in this age group.

Key Questions

KQ 1: What is the evidence for the effectiveness of treatments or combinations of treatments for binge eating disorder?

KQ 2: What is the evidence for harms associated with treatments for binge eating disorder?

KQ 3: Does the effectiveness of treatments for binge eating disorder differ by age, sex, race, ethnicity, initial body mass index, duration of illness, or coexisting conditions?

KQ 4: What is the course of illness of binge eating disorder?

KQ 5: Does the course of illness of binge eating disorder differ by age, sex, race, ethnicity, sexual orientation, body mass index, duration of illness, or coexisting conditions?

KQ 6: What is the evidence for the effectiveness of treatments or combinations of treatments for loss-of-control eating among bariatric surgery patients?

KQ 7: What is the evidence for harms associated with treatments for loss-of-control eating among bariatric surgery patients?

KQ 8: Does the effectiveness of treatments for loss-of-control eating among bariatric surgery patients differ by age, sex, race, ethnicity, initial body mass index, duration of illness, or coexisting conditions?

KQ 9: What is the course of illness of loss-of-control eating among bariatric surgery patients?

KQ 10: Does the course of illness of loss-of-control eating among bariatric surgery patients differ by age, sex, race, ethnicity, sexual orientation, initial body mass index, duration of illness, or coexisting conditions?

KQ 11: What is the evidence for the effectiveness of treatments or combinations of treatments for loss-of-control eating among children?

KQ 12: What is the evidence for harms associated with treatments for loss-of-control eating among children?

KQ 13: Does the effectiveness of treatments for loss-of-control eating among children differ by age, sex, race, ethnicity, initial body mass index, duration of illness, or coexisting conditions?

KQ 14: What is the course of illness of loss-of-control eating among children?

KQ 15: Does the course of illness of loss-of-control eating among children differ by age, sex, race, ethnicity, initial body mass index, duration of illness, or coexisting conditions?

Population(s):

- Individuals meeting either DSM-IV or DSM-5 criteria for binge eating disorder (BED)

- Post-bariatric surgery patients meeting criteria for loss-of-control (LOC) eating after surgery¹
- Children (6 years of age and older) meeting criteria for LOC eating²

Interventions:

Applies only to KQs on effectiveness and harms of BED treatment in adults (KQs 1, 2, and 3), LOC treatment in bariatric patients (KQs 6, 7, and 8), and LOC treatment in children (KQs 11, 12, and 13).

- Pharmacological interventions
 - Antidepressants:
 - Selective serotonin reuptake inhibitors (SSRIs)
 - Serotonin-norepinephrine reuptake inhibitors (SNRIs, excluding sibutramine because it is unavailable in the United States)
 - Norepinephrine reuptake inhibitors (NRIs)
 - Tricyclic antidepressants
 - Anticonvulsants (antiepileptics)
 - Weight loss drugs (orlistat)
 - Appetite suppressants (excluding rimonabant because it is unavailable in the United States)
 - Gamma-aminobutyric acid agonists
 - Mixed gamma-aminobutyric acid agonist/glutamate antagonists
 - Central nervous system stimulants
- Psychological or behavioral interventions
 - Cognitive behavioral therapy (CBT)
 - Interpersonal psychotherapy (IPT)
 - Dialectical behavior therapy (DBT)
 - Family-based therapy (for LOC eating in children and adolescents)
 - Parent training (for LOC eating in children and adolescents)
 - Behavioral weight loss interventions
 - Virtual reality therapy
 - Nutritional counseling or low-calorie diet (or both)
 - Exercise
 - Health education
- Complementary and alternative medicine (CAM) interventions
 - Nutraceuticals and dietary supplements
 - Acupuncture
- Combinations of pharmacotherapies; combinations of psychological interventions; combinations of CAM interventions; combinations of pharmacotherapy, psychological, behavioral, and/or CAM interventions
- Characteristics of interventions
 - Pharmacotherapy and CAM: dosages, duration of treatment

¹ Bariatric surgery patients may have had either BED or LOC eating diagnoses before surgery, but after surgery they are typically diagnosed only with LOC eating (i.e., loss-of-control eating behaviors without having consumed an unusually large amount of food).

² Children, especially those who are preadolescent, tend to be diagnosed only with LOC eating, not BED, in part because parents or others may limit the quantity of food they are permitted to consume.

- Psychological or behavioral: format (e.g., individual or group, therapist-led or self-help), frequency, duration of treatment

Comparators:

Applies only to KQs on effectiveness and harms of BED treatment in adults (KQs 1, 2, and 3), LOC treatment in bariatric patients (KQs 6, 7, and 8), and LOC treatment in children (KQs 11, 12, and 13).

- Placebo or usual care
- Any active intervention or combination of active interventions from among those listed above

Outcomes:

- Intermediate outcomes
 - Change in weight or body mass index (BMI) (or both)
 - Appetite-regulating peptide hormones
 - Blood lipids (cholesterol, triglycerides)
 - Blood glucose, hemoglobin A1c
 - Blood pressure
- Final health outcomes
 - Behavioral
 - Binge eating: frequency of binge episodes, frequency of binge days, binge abstinence
 - LOC eating: frequency of LOC eating episodes, LOC eating abstinence
 - Psychological
 - Shape and weight concerns, restraint, hunger, disinhibition
 - Depressive disorders and symptoms
 - Anxiety
 - Substance abuse
 - Physical health and functioning
 - BMI, weight status or stabilization
 - Hypertension
 - Type 2 diabetes, impaired glucose tolerance, insulin resistance
 - Dyslipidemia
 - Heart disease
 - Gastric reflux (gastroesophageal reflux disorder), gastroparesis, other gastrointestinal diagnoses or problems
 - Irritable bowel syndrome
 - Menstrual problems (female), hormonal problems (male or female)
 - Reproductive function
 - Social and occupational functioning
 - Work or school days lost
 - Marital or partner status
 - Quality of life: health-related quality of life or patient-reported outcomes not otherwise listed above
- Harms: Applies only to harms of treatment (KQs 2, 7, and 12)

- Pharmacotherapy and CAM: sedation, dry mouth, headache, nausea, insomnia, diarrhea, fatigue, increased urinary frequency, sexual dysfunction, abnormal dreams, sweating, palpitations, arrhythmia, cramping, diffuse pain, weight gain
- Psychological or behavioral therapy: negative effects of disclosing symptoms during initial evaluation or therapy
- Worsening of BED or LOC eating (or associated symptoms)
- Health care use and costs
 - Use of health care services: emergency room visits, hospitalizations (psychiatric hospitals, residential institutions, general hospitals), ambulatory physician visits (medical care, psychiatric care), ambulatory visits to other health care professionals (e.g., clinical psychologists), nutritional counseling
 - Costs of services: emergency room visits, hospitalizations (psychiatric hospitals, residential institutions, general hospitals), ambulatory physician visits (medical care, psychiatric care), ambulatory visits to other health care professionals, pharmacotherapies, and treatment costs for any harms

Timing:

- Treatment studies: no minimum duration
- Course of illness studies: 1-year minimum followup

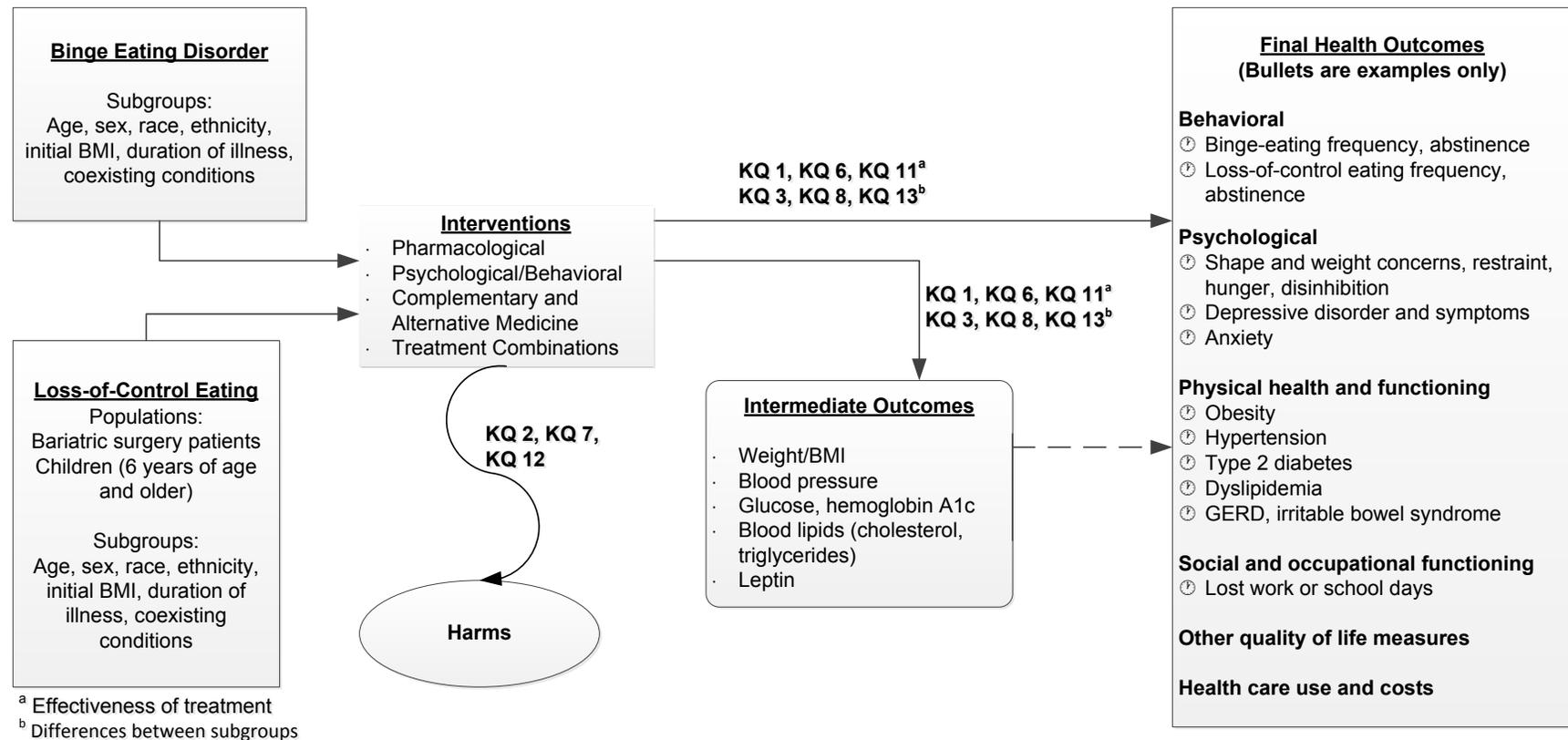
Settings:

- Inpatient, including hospitals and residential treatment centers
- Outpatient, including schools and homes

The relationship between the patient population, interventions, comparators, outcomes and timing of outcomes assessment (PICOTs) is depicted for each of the treatment KQs (Figure 1) and each of the course of illness KQs (Figure 2).

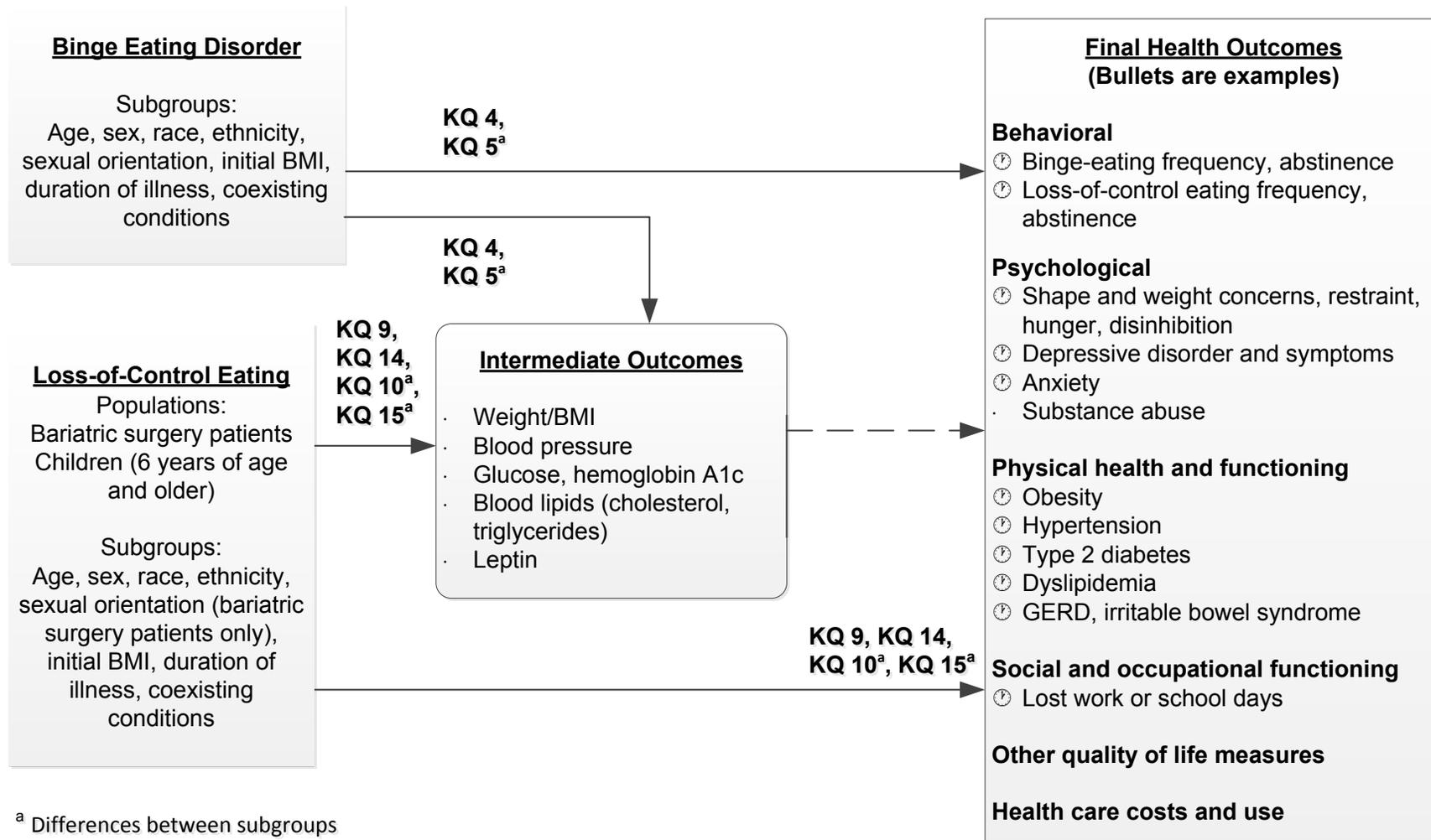
III. Analytic Framework

Figure 1. Analytic framework for binge eating disorder and loss-of-control eating: Effectiveness and harms of interventions



Abbreviations: BMI = body mass index; GERD = gastroesophageal reflux disease; KQ = Key Question; LDL = low density lipoprotein

Figure 2. Analytic framework for binge eating disorder and loss-of-control eating: Course of illness (outcomes of the disorders)



^a Differences between subgroups

Abbreviations: BMI = body mass index; GERD = gastroesophageal reflux disease; KQ = Key Question

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review: We specified our inclusion and exclusion criteria based on the populations, interventions, comparators (control intervention), outcomes, timing, and settings identified through the topic refinement exercise (Table 2). Our exclusion of non-English-language studies is based on limitations of time and resources. However, we will examine English language abstracts of non-English language studies to assess the potential size of the literature that would be missed through this approach. In relation to treatment studies, we will exclude study designs without control (or comparison) groups to ensure that our pool of included studies can inform the causal link between the intervention and outcomes. An important consideration in the evaluation of non-RCT studies of treatment or course of illness will concern adequate adjustment for prognostic factors. Because LOC eating has no agreed-upon definition, we will include studies of individuals with LOC eating based on the diagnostic criteria specified by each study author.

Table 2. Inclusion/exclusion criteria

Category	Criteria	
	Inclusion	Exclusion
Population	Individuals of all races, ethnicities, and cultural groups in one of three subpopulations: (1) meeting DSM-IV or DSM-5 criteria for BED; or (2) postbariatric surgery patients with LOC eating; or (3) children with LOC eating. Because LOC eating has no commonly accepted definition, studies included in the review may define LOC eating using different diagnostic criteria.	Co-occurring AN or BN BED only: <ul style="list-style-type: none"> Children, but will not exclude studies with adolescents LOC eating only: <ul style="list-style-type: none"> Co-occurring BED Children younger than 6 years of age Studies of RCTs with fewer than 10 participants and nonrandomized studies with fewer than 50 participants.
Geography	No limit	None
Date of search	Searches will go back until 1980; searches will be updated after the draft report goes out for peer review	None
Study duration	No limit	None
Settings	No limit; for treatment studies includes inpatient, outpatient, or home-based treatment settings for treatments such as self-help; course-of-illness studies include these setting and also community-based observation	None
Interventions	Pharmacological, behavioral, psychological, or CAM treatments or combinations as described in the PICOTS criteria	Pharmacological interventions not marketed in the U.S.
Control interventions	Any active intervention described in the PICOTS criteria, placebo, or usual care	Pharmacological interventions not marketed in the U.S.

Table 2. Inclusion/exclusion criteria (continued)

Category	Criteria	
	Inclusion	Exclusion
Outcomes	As described in the PICOTS criteria, intermediate and final health outcomes, treatment harms, and costs (e.g., health care cost and use, lost work days). Intermediate health outcomes will include biomarkers that can be linked directly to final physical health outcomes, such that an accumulation or worsening over time in that biomarker would result in the final health outcome.	Studies that do not include at least one of the outcomes listed in the PICOTS criteria.
Timing of outcome measurement	Treatment studies: end of treatment or later Course-of-illness studies: 1 year after study entry or later	Treatment studies: Outcome measurement prior to study completion only Course-of-illness studies: Outcome measurement less than 1 year post-study entry
Publication language	English	All other languages
Study design	Original research Eligible study designs include <ul style="list-style-type: none"> • RCTs • Nonrandomized controlled trials • Prospective cohort studies • Retrospective cohort studies • Case-control studies • Systematic review and meta-analyses 	<ul style="list-style-type: none"> • Case series • Case reports • Nonsystematic reviews • Studies of treatment benefits without a control or comparison group
Publication type	Any publication reporting primary data	Publications not reporting primary data

Abbreviations: AN = anorexia nervosa; BED = binge eating disorder; BN = bulimia nervosa; CAM = complementary and alternative medicine; DSM = Diagnostic Statistical Manual; LOC = loss of control; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RCT = randomized controlled trial

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions: We will systematically search, review, and analyze the scientific evidence for each KQ. We will take the following steps to perform the literature search. To identify articles relevant to each KQ, we will begin with a focused MEDLINE® search for eligible interventions using a combination of medical subject headings (MeSH®) and title and abstract keywords, limiting the search to human-only studies. We will also search the Cochrane Library, the International Pharmaceutical Abstracts database, EMBASE, AMED (Allied and Complementary Medicine Database), Academic First Search, PsycINFO, and CINAHL using analogous search terms. These searches will include RCTs and nonrandomized studies. We selected these databases based on preliminary searches and consultation with content experts. The search period will go back to 1980. We will conduct quality checks to ensure that the search identifies known studies (i.e., studies identified during topic nomination and refinement). If we do not identify the known studies, we will revise and rerun our searches.

In addition, we will search the “gray literature” for unpublished studies relevant to this review and will include studies that meet all the inclusion criteria and contain enough methodological information to assess risk of bias. Potential sources of gray literature include ClinicalTrials.gov, the World Health Organization’s International Clinical Trials Registry Platform, Health Services Research Projects in Progress, the National Institutes of Health Research Portfolio Online Reporting Tools, the Database of Promoting Health Effectiveness Reviews, the New York Academy of Medicine Grey Literature Report, and CMS.gov. The Scientific Resource Center of the Agency for Healthcare Research and Quality (AHRQ) will manage the process of submitting requests for scientific information packets, which contain information about drugs, CAM interventions, or psychological interventions.

To avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that our electronic searches might have missed.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. We will investigate any literature the TEP, peer reviewers or the public suggest and, if appropriate, will incorporate additional studies into the final review. The appropriateness of those studies will be determined using the methods described above.

We will include pooled estimates of effect or other relevant results from systematic reviews that meet our inclusion/exclusion criteria. We will evaluate the quality of included systematic reviews using the AMSTAR tool.⁶³ As appropriate, we may update the results of these reviews quantitatively or qualitatively. Should identified reviews use inclusion/exclusion criteria that differ from ours, we will review their reference lists to ensure that we include all relevant studies.

Data Abstraction and Data Management: Two trained research team members will independently review all titles and abstracts identified through searches for eligibility against our inclusion/exclusion criteria. Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. We will track all results in an EndNote[®] bibliographic database (Thomson Reuters, New York, NY).

We will retrieve and review the full text of all titles included during the title/abstract review phase. Two trained team members will independently review each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, we will exclude the study. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. As described above, all results will be tracked in an EndNote database. We will record the reason that each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract important information into evidence tables. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions,

comparators, study designs, methods, and results. The forms will be compatible with criteria for inclusion in AHRQ's Systematic Review Data Repository. Trained reviewers will extract the relevant data from each included article into the evidence tables. A second member of the team will review all data abstractions for completeness and accuracy.

Assessment of Methodological Risk of Bias of Individual Studies: To assess the risk of bias (internal validity) of studies, we will use predefined design-specific criteria based on guidance provided by AHRQ.⁶⁴ We will evaluate the risk of bias of RCTs using A Cochrane Risk of Bias Assessment Tool (ACROBAT) designed for RCTs.⁶⁵ For non-RCTs, we will use a tool developed by Viswanathan et al.⁶⁶ modified by an ACROBAT-NRS tool this is currently under development.

In general terms, results of a study with low risk of bias are considered to be valid. A study with medium risk of bias is susceptible to some bias but probably not sufficient to invalidate its results. A study with high risk of bias has significant methodological flaws (i.e., stemming from serious errors in design or analysis) that may invalidate its results. We will consider the risk of bias for each relevant outcome of a study.

Two independent reviewers will assess the risk of bias for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team. We will rate studies that meet all criteria as having "low risk of bias." "Medium risk of bias" ratings will be given to studies where raters have some confidence that the results represent the true treatment effect; that is, although the study is susceptible to some bias, the problems are not considered sufficient to invalidate the results (i.e., no flaw is likely to cause major bias). We will give a "high risk of bias" rating to studies that have a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories.

Data Synthesis: For bodies of evidence that include non-RCTs we will synthesize the data qualitatively. If we find three or more similar RCTs for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. We will also consider conducting mixed treatment comparisons meta-analysis using Bayesian methods to compare interventions with one another if we identify a sufficient number of studies with a common comparator (e.g., placebo). For all analyses, we will use random-effects models to estimate pooled or comparative effects.

To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.⁶⁷ We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences.

If we conduct quantitative syntheses (i.e., meta-analysis), we will assess statistical heterogeneity in effects between studies by calculating the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity). The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p-value from the chi-squared test, or a confidence interval for I^2). If we include any meta-analyses with considerable statistical heterogeneity in this report, we will provide an explanation for doing so, considering the magnitude and direction of effects. We will also examine potential

sources of heterogeneity using sensitivity analysis or analysis of subgroups. We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate to examine clinical heterogeneity.

For any quantitative analyses, we will conduct sensitivity analyses, including high-risk-of-bias studies. The weight that we will give to high-risk-of-bias studies will be based on the perceived potential bias in the results from each of these studies. Planned stratifications or categories for subgroup analyses include the subgroups listed in the analytic framework and geographic location of studies. When quantitative analyses are not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

Grading the Strength of Evidence for Individual Comparisons and Outcomes: We will grade the strength of evidence based on the updated guidance established for the Evidence-based Practice Center (EPC) program.⁶⁸ Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: study limitations (includes study design and aggregate risk of bias), consistency, directness, precision of the evidence, and reporting bias. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).

Grades reflect the strength of the body of evidence to answer KQs included in this review (see Table 3). Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus. Senior members of the review team (including at least one subject matter expert and one methodologist) will grade the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those most commonly reported in the literature.

Table 3. Definitions of the grades of overall strength of evidence⁶⁸

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion

Assessing Applicability: We will assess applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.⁶⁹ We will use the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled populations, sex of enrolled populations (e.g., fewer men may be enrolled in the studies), and race or ethnicity of enrolled populations.

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

Not applicable.

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 ensure that the questions are specific and explicit about what information is being reviewed. In addition, the Key Questions were posted for public comment and put into final form 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 health care 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 Task Order Office and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute 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 healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and 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 or contribute to the writing of the report; they 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. In preparing the final draft of the report, the EPC considers all peer review comments on the preliminary draft. 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 comparative effectiveness reviews and technical briefs, be published 3 months after the publication of the Evidence report.

Potential Peer 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.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that total more than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHS A290201200008I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.