

## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Treatment of Depression During Pregnancy and the Postpartum Period

#### I. Background and Objectives for the Systematic Review

Women experience mood disorders at a high rate, with a 21.3 percent lifetime prevalence that peaks during the reproductive years.<sup>1</sup> The incidence of depression during pregnancy and the postpartum period is estimated to be anywhere from 5.5 to 33.1 percent.<sup>2,3</sup> During the postpartum period, up to 85 percent of women experience some type of mood disturbance; the American Academy of Pediatrics estimates that more than 400,000 infants are born each year to mothers who are depressed.<sup>4</sup>

Depression during pregnancy is known to lead to harmful prenatal health behaviors such as poor nutrition, poor prenatal medical care, smoking, alcohol or other substance misuse, and risk of suicide, each of which compromises the health of both the woman and her fetus.<sup>5,6</sup> Several adverse obstetric complications have been reported with untreated prenatal stress and depression, including pre-eclampsia, preterm delivery, low birth weight, miscarriage, small-for-gestational-age babies, low Apgar scores, and neonatal complications.<sup>7,8</sup> In addition to being debilitating for the mother, postpartum depression affects maternal-infant interactions and some measures of infant development; in extreme cases it may increase the risk of infant mortality through neglect, abuse, or homicide.<sup>9</sup> It also negatively affects interactions within other members of the family unit and is associated with intimate partner violence.<sup>10</sup>

Unipolar and bipolar depression during pregnancy and the postpartum period have a range of presentations including continuation or relapse of a pre-existing mood disorder, the development of changes in mood during pregnancy and the postpartum period, and the postpartum “baby blues.” Differentiating the correct diagnosis can be complex. Problems with mood are often accompanied by comorbid anxiety and occasionally by potentially life-threatening psychosis.<sup>11</sup>

General risk factors for depression include female sex, previous depression, a family history of depression, poor social support, and substance abuse. Additional factors associated with depression in pregnant women include younger age, non-Latino ethnicity, being without a partner, traumatic events within the previous 12 months, and pregnancy complications.<sup>1,3</sup>

Management of mood disorders in pregnancy varies case by case. In women with existing mood disorders, the tactic may be to stabilize the mood disorder before attempting pregnancy. But providers and patients are often concerned about the safety of continued pharmacological treatment to the fetus during pregnancy and the postpartum period.<sup>12</sup> This makes information about the comparative effectiveness of nonpharmacological treatments during pregnancy of high interest. In women with emerging mood disorders during pregnancy and the postpartum period, it can be important to distinguish the correct diagnosis because treatments may vary—for example, while an antidepressant may be an appropriate treatment for major depressive disorder, it could potentially trigger mania in people with bipolar disorder. Bipolar disorder may also dispose the mother to a greater risk of postpartum psychosis.

Interventions for depression in the postpartum period can include pharmacological treatments, nonpharmacological treatments, and watchful waiting or no intervention. Pharmacological treatments approved by the U.S. Food and Drug Administration (FDA) for

depression and bipolar disorder in the depressed or mixed phases are listed in Table 1. There are also a wide array of nonpharmacological interventions that can be used to treat depression in the postpartum period including various psychotherapies, electroconvulsive therapy, transcranial magnetic stimulation, and acupuncture, among others.<sup>13</sup>

The objective of this systematic review is to compare the effectiveness of various treatment options, both pharmacological and nonpharmacological, for perinatal depression in women. Factors (patient, provider, or environmental) that might impact maternal and child outcomes during treatment of perinatal depression will be assessed. Negative effects of untreated disease and exposure to antidepressive drugs will be evaluated, highlighting the treatment dilemmas confronting women with perinatal depression. Finally, we will identify issues that future studies should address so that the woman with perinatal depression, health care providers, and other stakeholders can make optimally informed decisions.

## II. The Key Questions

The Agency for Healthcare Research and Quality (AHRQ) wrote preliminary Key Questions (KQs) based on input from the topic nominator. The Pacific Northwest Evidence-based Practice Center (PNW EPC) revised the KQs and developed eligibility criteria to identify the populations, interventions, comparators, outcomes, timing, and study designs of interest. The PNW EPC further refined the KQs and eligibility criteria based on input from the AHRQ representatives during a project kickoff call. The PNW EPC solicited additional input from the Technical Expert Panel (TEP). Refinements of note include:

- **Population:** We clarified that the scope includes treatment of subthreshold depressive symptoms and added treatment during the time of conception. We clarified that anxiety will be considered as occurring as a symptom of depression or as a comorbidity. The report will not address women with anxiety as a diagnosis without depression. The TEP suggested that bipolar depression be excluded from this report, as it was felt that a review of this condition should include all aspects of the disease (mania, psychosis).
- **Interventions:** As a result of the change in population (above) the scope of interventions was narrowed to include commonly used antidepressant medications. The examination of combination therapy was expanded to include studies comparing drug + nondrug interventions that are compared with drug only interventions.
- **Outcomes:** We clarified that anxiety as a specific symptom will be addressed, using a specific subquestion. Additional outcomes were suggested by the TEP, including infant attachment and child interaction with the criminal justice system.
- **Study designs:** We expanded the scope to include observational evidence for benefits in cases where randomized trial evidence is insufficient and to include interrupted time-series studies for both benefits and harms.

The revised KQs are as follows:

### Question 1

What are the comparative benefits of pharmacological and nonpharmacological



treatments for women with depression during pregnancy and in the postpartum period?

- a. How do pharmacological treatments affect maternal and child\* outcomes when compared with placebo or no active treatment or usual care?
- b. How do pharmacological treatments affect maternal and child outcomes when compared with each other (drug A vs. drug B)?
- c. How do pharmacological treatments affect maternal and child outcomes when compared with active nonpharmacological treatments?
- d. How does combination therapy affect maternal and child outcomes? The combinations include:
  - i. Using a second drug to augment the effects of the primary drug and comparing this treatment with monotherapy with a single drug
  - ii. Combining pharmacological treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone
  - iii. Comparing pharmacological treatments alone with pharmacological treatments used in combination with nonpharmacological treatments

\*A child is defined as a fetus, infant, or a child up to age 18.

## Question 2

- a. What are the comparative harms of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?
  - i. How do pharmacological treatments affect maternal and child\* outcomes when compared with placebo or no active treatment or usual care?
  - ii. How do pharmacological treatments affect maternal and child outcomes when compared with each other (drug A vs. drug B)?
  - iii. How do pharmacological treatments affect maternal and child outcomes when compared with active nonpharmacological treatments?
  - iv. How does combination therapy affect maternal and child outcomes? The combination include:
    - (a) Using a second drug to augment the effects of the primary drug and comparing this treatment with monotherapy with pharmacological treatment
    - (b) Combining pharmacological treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone
    - (c) Comparing pharmacological treatments alone with pharmacological treatments used in combination with nonpharmacological treatments
- b. In babies born to women who become pregnant while taking medications to treat



depression, what is the comparative risk of teratogenicity?

\*A child is defined as a fetus, infant, or a child up to age 18.

### Question 3

Is there evidence that the comparative effectiveness (benefits or harms) of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period varies based on characteristics\*\* such as:

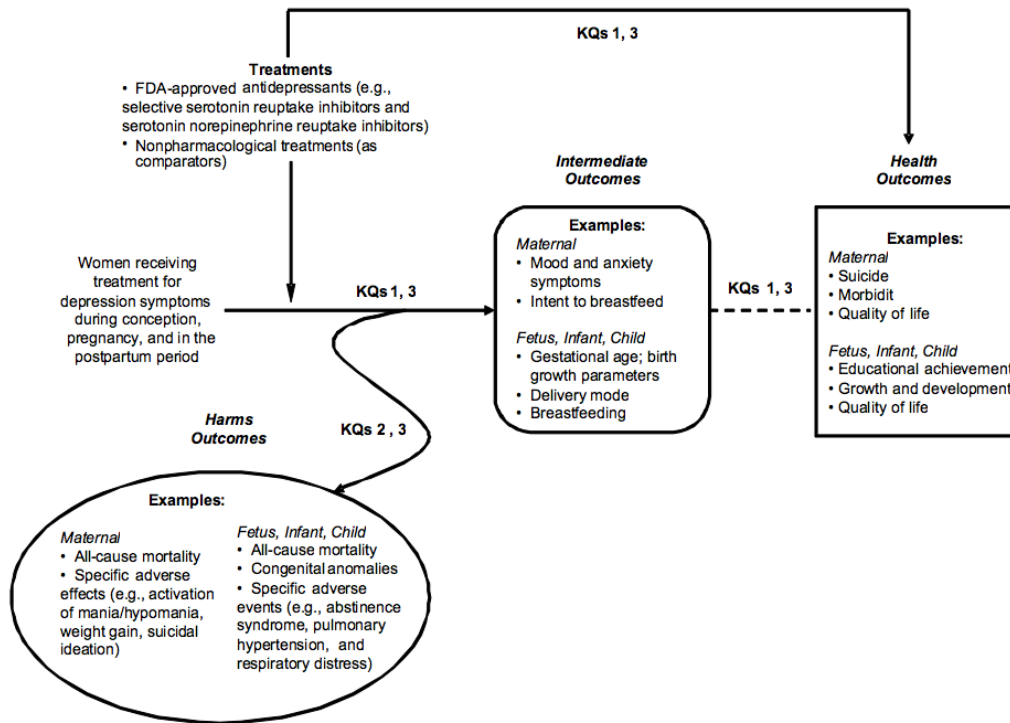
- a. Patient characteristics—race, age, socioeconomic status, family history of depressive/mood disorders, prior use of antidepressive drugs (for treatment or prevention), severity of symptoms, situation at home, unplanned pregnancy, and marital/partner status?
- b. Patient comorbidities (e.g., anxiety diagnoses)?
- c. Intervention characteristics—dosing regimens and duration of treatments?
- d. Coadministration of other psychoactive drugs, specifically, antipsychotics, antianxiety agents (e.g., benzodiazepines), and drugs for insomnia?
- e. Medical provider characteristics (primary care physician, obstetrician, psychiatrist, nurse, midwife, community worker, or pediatrician visits)?
- f. Medical care environment (community/private/public clinic or hospital)?
- g. Characteristics of diagnosis—whether depression was detected during screening or not, time of diagnosis, method of diagnosis, and when treatment commenced relative to the onset of symptoms?

\*\*Other factors will be considered as they are identified within the comparative studies.

### III. Analytic Framework

The analytic framework below illustrates the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis.

**Figure 1. Analytic framework**



\*The full lists of interventions and outcomes are too extensive to illustrate in their entirety in this diagram. See the inclusion criteria for the full list of interventions and outcomes.  
 FDA = U.S. Food and Drug Administration; KQ = key question

## IV. Methods

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

The PNW EPC developed preliminary inclusion/exclusion criteria, identifying populations, interventions, comparators, outcomes, timing, settings, and study designs of interest, and revised them based on input from AHRQ representatives on the kickoff call. The PNW EPC will seek additional input from the TEP. The following inclusion/exclusion criteria reflect revisions made following the kickoff call:

#### Inclusion Criteria

##### Populations

Pregnant women and women during the first 12 months after delivery, who are receiving treatment for a depressive episode, including:

- Those who meet the diagnosis for major depressive disorder as described in the 4th

edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

- Subthreshold depressive symptoms which have become the subject of clinical attention.
- Exclusions: Those who meet DSM-IV diagnosis for bipolar depression, psychotic depression, a mood disorder secondary to a general medical condition, or a mood disorder secondary substance abuse.

## Interventions

Interventions include commonly used antidepressant drugs. Drugs not listed below will not be included (e.g., monoamine oxidase inhibitors).

**Table 1. Interventions**

Antidepressant agents by classification	Generic Name	Trade Name
Selective serotonin reuptake inhibitor	Citalopram	Celexa <sup>®</sup> (various generics)
	Escitalopram	Lexapro <sup>®</sup>
	Fluoxetine	Prozac <sup>®</sup> (various generics) Prozac Weekly <sup>®</sup> Sarafem <sup>®</sup>
	Fluvoxamine	Luvox <sup>®</sup> (various generics)
	Sertraline	Zoloft <sup>®</sup> (various generics)
	Paroxetine	Paxil <sup>®</sup> (various generics) Paxil CR <sup>®</sup>
	Vilazodone	Viibryd <sup>®</sup>
Serotonin norepinephrine reuptake inhibitor	Desvenlafaxine	Pristiq <sup>®</sup>
	Venlafaxine	Effexor <sup>®</sup> Effexor XR <sup>®</sup>
Noradrenergic and specific serotonergic reuptake inhibitor	Mirtazapine	Remeron <sup>®</sup> (various generics)
Selective serotonin and norepinephrine reuptake inhibitor	Duloxetine	Cymbalta <sup>®</sup>
Norepinephrine and dopamine reuptake inhibitor (NDRI)	Bupropion	Wellbutrin <sup>®</sup> Wellbutrin SR <sup>®</sup> Wellbutrin XL <sup>®</sup>
5-HT <sub>2</sub> receptor antagonist	Nefazodone	Serzone <sup>®</sup>
Tricyclic Antidepressants	Amitriptyline	Various generics
	Desipramine	Norpramin and various generics
	Imipramine	Presamine and various generics
	Nortriptyline	Various generics

## Comparators

- Placebo or no treatment
- Usual care: We will define usual care as receiving pregnancy and postpartum care similar to those with normal risk pregnancies. When “usual care” is the comparator two reviewers with experience in delivering postpartum health care (JR and JMG) will separately determine if it is “usual,” and if they believe it not to be usual it will be included as a separate “greater than usual care” comparator.
- The drugs listed above in Table 1 when compared with each other.
- Other active pharmacological treatments used to augment drugs with an FDA indication for unipolar or bipolar depression.



- Any nonpharmacological treatment, including but not limited to over-the-counter treatments, osteopathic or naturopathic treatments, herbal remedies and vitamins, all forms of psychotherapy, case management, electroconvulsive therapy, nonrepetitive and repetitive transcranial magnetic stimulation, vagal nerve stimulation, exercise, meditation, and touch therapies.

## **Efficacy/ Effectiveness Outcomes**

### **Maternal**

- Danger to self (suicidal and nonsuicidal behaviors)
- Danger to infant (infanticidal behavior, abuse, or neglect)
- Depression symptomatology as scored using validated scales measuring depression
  - Response
  - Remission
  - Speed and duration of response/remission
  - Relapse
  - Recurrence
  - Change in core depressive symptoms
- Anxiety symptoms as scored as a subscale item using validated scales measuring depression, or validated scales used to measure anxiety symptoms
- Functional capacity
  - Quality of life using validated scales, for example, Medical Outcomes Survey 36-item Short Form (SF-36)
  - Caring for self, infant and family
  - Mother-father dyad interaction success, including reduced violence among intimate partners
  - Work productivity
- Delivery and postpartum parameters
  - Breastfeeding
  - Shared decision making around delivery choices (e.g., cesarean)
  - Delivery mode
  - Mother-infant dyad interaction patterns
  - Pregnancy weight gain within or outside of 1990 Institute of Medicine Guidelines
- Social services utilization
  - Prevention of child protective service involvement.
- Maternal health system resource utilization including emergency department use, hospitalizations, and office visits
- Adherence or persistence with treatment regimen

### **Fetus, Infant, Child**

- Parameters at birth and up to 12 months of age:
  - Preterm birth (e.g., < 32 weeks, < 37 weeks)
  - Appropriate growth (height, weight, and head circumference)



- Gestational age (e.g., small for gestational age), race/ethnicity taken into consideration
- Birth hospitalization length of stay
- Infant attachment
- Developmental screening—Ages and Stages Questionnaire; Denver; Modified Checklist for Autism in Toddlers; Bayley Scales of Infant Development
- Growth and development after 1 year of age:
  - Developmental screening and diagnoses
  - Growth parameters (height, weight, and body mass index percentile according to sex and age)
- Learning (e.g., linguistic, cognitive, and social-emotional skills) and educational achievement
  - Kindergarten readiness
  - Age at Kindergarten entry
  - Third grade testing outcomes
  - Other standard testing outcomes (Eighth grade, etc)
  - Intelligence tests (any)
  - Individualized education plans/use of school services
  - School failure/dropout rate
  - High school graduation rate
  - Missed school days
- Stress-related chronic disease
  - Mental illness
  - Chronic illness
- Infant health system visits (e.g., well baby visits)
  - Health care utilization (primary care, emergency department, hospitalization)
- Social services utilization (Women, Infants, and Children Program [WIC], community health nurse, social worker, State Department of Health and Human Services, free and reduced lunch, and food stamps)
  - Community resource utilization (community engagement measures)
- Social and emotional development
- Quality of life
- Contact with juvenile justice system.

## Harms

### Maternal

- Death (including suicide, all-cause mortality and cause-specific [e.g., cardiac] death)
- Specific adverse effects or withdrawals due to specific adverse events related to treatment (e.g., hyponatremia, activation of mania/hypomania, seizures, suicidal ideation, hepatotoxicity, weight gain, metabolic syndrome, gastrointestinal symptoms, and loss of libido)
- Overall adverse-event reports
- Withdrawals from study and discontinuation of treatment due to adverse events





- Adverse events associated with discontinuation of treatment
- Serious adverse events reported

### **Fetus, Infant, and Child**

- All-cause mortality
- Congenital anomalies (any)
  - Stratified into major and minor with further grouping by organ system or type of anomaly
- Other specific adverse events (e.g., withdrawal symptoms [neonatal abstinence symptoms], pulmonary hypertension, respiratory distress, neonatal convulsions, and heart defects)

### **Timing**

- All followup periods are eligible.

### **Setting**

Studies conducted in economically advanced countries will be included ([www.imf.org/external](http://www.imf.org/external)). These countries are: Australia, Austria, Belgium, Canada, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Iceland, Ireland, Israel, Italy, Japan, South Korea, Luxembourg, Malta, The Netherlands, New Zealand, Norway, Portugal, Singapore, the Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Taiwan, the United Kingdom, and the United States of America.

### **Study Designs**

- For efficacy or effectiveness, a “best evidence” approach will be used. Randomized controlled clinical trials and systematic reviews of such trials will be included as the top-tier evidence. If insufficient evidence is found with this study design, we will explore observational study evidence (defined as cohort studies comparing at least two concurrent treatment groups, case-control studies, and time-series studies).
- For harms, in addition to randomized controlled clinical trials and systematic reviews, observational studies (defined as cohort studies comparing at least two concurrent treatment groups, case-control studies, and time-series studies) will be included.
- For systematic reviews, we will only include those that (1) search at least two databases and (2) discuss methodology of quality assessment and data abstraction. In accordance with established methodologies, systematic reviews will be used in place of de novo analysis and synthesis of the included studies wherever possible, depending on the details of how closely the review matches the report scope and how recent the review is.<sup>14, 15</sup>  
Exclusions: case reports, case series, and single-group studies.

The PNW EPC will use the inclusion/exclusion criteria outlined above to select eligible studies. Additionally, the PNW EPC plans to limit inclusion to only studies published in the English language due to resource and timeline constraints. The PNW EPC expects that excluding studies published in languages other than English will have little effect on the review findings as

it is likely that the majority of the literature on this topic is published in English. Studies published from 1955 and after will be included.

Titles and abstracts will first be assessed by one reviewer, with a second reviewer assessing only those titles and abstracts that the first reviewer deemed ineligible. Full-text articles of all potentially relevant titles and abstracts will be retrieved and will be assessed by two independent reviewers. Disagreements will be resolved by consensus of the two reviewers.

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

To identify articles relevant to each KQ, the librarian will search the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Cumulative Index to Nursing and Allied Health Literature (CINAHL<sup>®</sup>), MEDLINE<sup>®</sup>, PsychINFO<sup>®</sup>, and Scopus. A sample MEDLINE search strategy appears in Table 2. We will not place date restrictions on database searches. Grey literature will be identified by searching clinical trial registries (ClinicalTrials.gov, WHO Trial Registries) and the Web sites of individual funders. Scientific Information Packets will be solicited from industry stakeholders through the Scientific Resource Center.

**Table 2. Sample Ovid MEDLINE<sup>®</sup> search strategy**

Concept	Search String	Citations
<b>Population: pregnant women</b>	exp Pregnancy/ or Perinatal Care/ or Postnatal Care/ or Postpartum Period/ or exp Postpartum Period/ or Prenatal Care or Preconception Care or (pregnan\$ or perinatal or postpartum).mp	n = 793,613
<b>Population: offspring of women treated for depression or other mood disorders during pregnancy</b>	(exp Prenatal Injuries/ or exp Maternal Exposure/ or exp Pregnancy Complications/ or exp Pregnancy Outcome/ or exp Fetal Development/) and (exp Infant/ or exp Infant Mortality/ or exp child/ or exp child, preschool/ or (infant\$ or child\$ or pediatri\$).mp) or (Abnormalities, Drug-Induced or Prenatal Exposure Delayed Effects or teratogen\$)	n = 164,643
<b>Condition</b>	(mood disorders/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or Depression/ or (depressi\$ or dysthymi\$ or "mood disorder\$" or "seasonal affective disorder" or sad).mp) and (de or dh or dt or pc or th).fs	n = 141,908
<b>Interventions</b>	Serotonin Uptake Inhibitors/ or (selective serotonin reuptake inhibitor\$ or ssri).mp or (citalopram or escitalopram or fluoxetine or fluvoxamine or sertraline or paroxetine).mp or (celexa or lexapro or prozac or luvox or zoloft or paxil).mp. or "serotonin norepinephrine reuptake inhibitor".mp or (desvenlafaxine or mirtazapine).mp or (pristiq or effexor).mp or ("noradrenergic and specific serotonergic reuptake inhibitor").mp or mirtazapine.mp or remeron.mp or ("selective serotonin and norepinephrine reuptake inhibitor").mp or ssnri.mp or (duloxetine or cymbalta).mp or ("norepinephrine and dopamine reuptake inhibitor").mp or ndri.mp or (bupropion or wellbutrin).mp or (nefazodone or serzone).mp or (olanzapine adj1 fluoxetine).mp or exp Antidepressive Agents/ or Antidepressive Agents, Tricyclic/ or (amitriptyline or imipramine or desipramine or nortriptyline).mp	n = 126,267
	<b>Term combination 1 Population: pregnant women + condition + interventions</b>	n = 1,087
	<b>Term combination 2 Population: offspring of women for depression or other</b>	n = 1,103

	<b>mood disorders during pregnancy + interventions</b>	
	<b>Term combination 1 or 2</b>	n = 2,190
	<b>Methods limit: humans, English language publication or English language abstract</b>	n = 2,020

All above-described electronic searches will be updated when the draft report is posted for public comment and sent to peer reviewers.

Regardless of publication status, any additional studies identified during public and peer review—found from the updated literature search or found in the grey literature or Scientific Information Packets will be reviewed for inclusion using the same study selection process described above. The PNW EPC will include supplemental unpublished data (e.g., additional outcomes and analyses) relating to a published study only if the following details of the analysis are provided: type of statistical test used, numbers analyzed, and whether an intention-to-treat analysis was conducted. Study authors will be contacted for additional data only related to key outcomes and only when we are missing data necessary for a meta-analysis.

### C. Data Abstraction and Data Management

The following data will be abstracted from included studies: design; setting (community/private/public clinic, hospital); population characteristics (race, age, socioeconomic status, family history of depressive/mood disorders, prior use of antidepressive drugs, severity of symptoms, situation at home, unplanned pregnancy, marital/partner status, comorbidities); eligibility and exclusion criteria; characteristics of diagnosis (whether depression was detected during screening or not, time of diagnosis, method of diagnosis, and when treatment commenced relative to the onset of symptoms); intervention characteristics (dose, duration, and cointerventions); comparisons; medical provider characteristics (primary care physician, obstetrician, psychiatrist, nurse, midwife, community worker, and pediatrician visits); numbers of patients screened, eligible, enrolled, and lost to followup; method of outcome ascertainment; and results for each outcome. One reviewer will abstract study data, and a second reviewer will review abstractions. Intention-to-treat results will be recorded if available.

### D. Assessment of Methodological Risk of Bias of Individual Studies

The internal validity (quality) of systematic reviews, randomized trials, and cohort and case control studies will be assessed based on predefined criteria established by the Drug Effectiveness Review Project.<sup>14</sup> For trials, these criteria were based initially on the criteria used by the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom).<sup>16,17</sup> In rating the internal validity of trials, we evaluate methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis.

The internal validity of observational studies will be rated based on the adequacy of the patient selection process; whether there was important differential loss to followup or overall high loss to followup; the adequacy of event ascertainment; whether acceptable statistical techniques were used to minimize potential confounding factors; and whether the duration of followup was reasonable to capture investigated events.

The internal validity of systematic reviews will be rated based on a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies.

All assessments will be done at the overall study level and will result in a rating of good, fair, or poor. Studies that have a fatal flaw will be rated poor in quality; studies that meet all criteria will be rated good in quality; the remainder will be rated fair in quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality study is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared interventions. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist.

All studies will first be rated by one reviewer and then checked by another reviewer. All disagreements will be resolved using a consensus process.

## **E. Data Synthesis**

Evidence tables will be constructed to show the study characteristics, quality ratings, and results for all included studies. A hierarchy-of-evidence approach will be used, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Data from poor-quality studies will generally be excluded from the synthesis but will be presented in evidence tables for transparency.

To determine the appropriateness of meta-analysis, the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes will be considered. Appropriate measures will be chosen based on the type of data for meta-analysis. The Q statistic and the I<sup>2</sup> statistic (the proportion of variation in study estimates due to heterogeneity) will be calculated to assess heterogeneity in effects between studies.<sup>18,19</sup> Random-effects models will be used to estimate pooled effects.<sup>20</sup> Statistical heterogeneity will be explored by using subgroup analysis or meta-regression. Forest plots will be used when applicable to graphically summarize the results of individual studies and of the pooled analysis.<sup>21</sup>

When meta-analysis cannot be performed, the data will be summarized qualitatively, grouping studies by similarity of population and/or intervention characteristics.

## **F. Grading the Strength of Evidence for Individual Outcomes**

We will use the methods outlined in chapter 10 of the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*<sup>22</sup> (an edited version of the chapter has also been published in the *Journal of Clinical Epidemiology*<sup>23</sup>) to grade strength of evidence. Domains considered in grading the strength of evidence include consistency, directness, precision, and risk of bias. Based on this assessment, the body of evidence will be assigned a strength-of-evidence grade of high, moderate, or low. In cases where evidence does not exist, is sparse, or contains irreconcilable inconsistency, a grade of insufficient evidence will be assigned. Technical experts were consulted to help inform prioritization of the outcomes for grading. Specific outcomes and comparisons to be rated will depend on the evidence found in the literature review.

## G. Assessing Applicability

Applicability will be assessed by paying special attention to study eligibility criteria, characteristics of the enrolled population in comparison to the target population, characteristics of the intervention and comparator used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. Technical experts identified items of particular interest that may contribute to heterogeneity and impact applicability. In general, these will include the subgroups specified in KQ 4: population characteristics (race, age, socioeconomic status, family history of depressive/mood disorders, prior use of antidepressive drugs, severity of symptoms, situation at home, unplanned pregnancy, and marital/partner status), comorbid anxiety diagnoses and other comorbidities, characteristics of diagnosis (whether depression was detected during screening or not, time of diagnosis, method of diagnosis, and when treatment commenced relative to the onset of symptoms), intervention characteristics (dose, duration, and cointerventions), comparisons, and medical provider characteristics (primary care physician, obstetrician, psychiatrist, nurse, midwife, community worker, and pediatrician visits). We will summarize issues of applicability qualitatively.

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## VI. Definition of Terms

Not applicable.

## 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.

Below is an example table:

Date	Section	Original Protocol	Revised Protocol	Rationale

## VIII. Review of Key Questions

For all EPC reviews, Key Questions were reviewed and refined as needed by the EPC with input from the TEP to assure that the questions are specific and explicit about what information is being reviewed.

## IX. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and in 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/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 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.

## X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological 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

Comparative Effectiveness Reviews and Technical Briefs, be published 3 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.

## **XI. EPC Team Disclosures**

No team member disclosed potential financial conflicts of interest.

## **XII. Role of the Funder**

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