Evidence-based Practice Center Systematic Review Protocol

Project Title: *Comparative Effectiveness of Progestogens for the Prevention of Preterm Birth*

I. Background and Objectives for the Systematic Review

Background

Preterm birth is the delivery of an infant before the completion of 37 weeks of gestation. Preterm births contribute to more than 85% of all perinatal morbidity and mortality and are the leading cause of infant mortality and long-term disability.[1,2] In 2004, for example, more than 480,000 infants were born prematurely in the United States, representing 12.5% of live births.[3] Efforts to combat premature birth in the United States have been largely unsuccessful, as evidenced by a 20% increase in the proportion of preterm births since 1990.[2]

The morbidity and mortality associated with preterm birth represent untold distress for families, as well as significant costs to patients, health care systems, and payers. Mean neonatal costs are estimated to be $17,300 (in 2004 dollars) greater for preterm infants relative to term infants, amounting to more than $8.6 billion of annual medical spending in the United States.[4] Preterm birth occurs disproportionately in populations of low socioeconomic status, and because many public programs target these populations the costs of preterm birth in the public arena are substantial. It is estimated that 40% of the medical costs associated with preterm births are paid by Medicaid.[1]

The publication of a recent report by the Institute of Medicine titled *Preterm Birth: Causes, Consequences, and Prevention*, reflects substantial public interest in preterm birth. The report identifies critical gaps in our knowledge, particularly with regard to identifying and treating women at high risk for preterm birth; and proposes areas for future research.[1] To underscore the importance of the problem, in 2006 the United States Congress passed the Prematurity Research Expansion and Education for Mothers who deliver Infants Early (PREEMIE) Act (P.L. 109-450).[5] The purposes of this Act include 1) reducing rates of preterm labor and delivery; 2) working toward an evidence-based standard of care for pregnant women at risk of preterm labor or other serious complications and for infants born preterm and at a low birthweight; and 3) reducing infant mortality and disabilities caused by prematurity.

This Act also mandated a Surgeon General's Conference on the Prevention of Preterm Birth, which was held in 2008, to address persistent concerning trends in preterm birth.[6] One of the recommendations was to offer 17-alphahydroxyprogesterone caproate (17-OHP) to women with a history of preterm birth. The Biomedical Research Workgroup made a recommendation that further research on 17-OHP be supported, including its mechanism of action, clinical indications, optimal forms, dosing, and safety.[7] Recently published evidence based on systematic reviews and meta-analyses of randomized controlled trials indicates that 17-OHP is effective in the prevention of recurrent spontaneous preterm births.[8,9] Other progestogens may also be effective. Until these trials on the use of progesterone were published, no other generally effective therapy had been shown to prevent preterm birth.[9] Progesterone is a hormone that inhibits the uterus from contracting and is involved in maintaining pregnancy, especially early in gestation; the mechanism by which it acts later in pregnancy is not well understood.

In the United States, approximately 133,000 expectant mothers annually have a history of preterm birth and are good candidates for progestogens; the treatment of this population could prevent 10,000 preterm births annually.[4] Rates of preterm birth are higher among low-income and other vulnerable populations, and thus a larger ratio of this population relative to the general population may benefit from progestogen treatment.

A recent study to assess the impact of a specific progestogen treatment, 17-OHP, on future medical costs for expectant mothers with a prior preterm birth found that there is the potential for cost savings that substantially exceed the cost of treatment.[10] The cost of a typical 17-OHP treatment regimen is relatively modest; one study estimates it to be about $400 per treated patient.[10] This estimate factors in the cost of each dose of drug, the number of injections needed, and the hourly wage of a registered nurse needed to administer the injections. If all at-risk pregnant women were treated with 17-OHP, the aggregate medical cost savings could be substantial. The cost of treating eligible women would be approximately $53 million annually, and is projected to reduce initial neonatal medical costs by more than $505 million each year; annual net savings, then, are estimated to be $452 million, and over the lifetime of affected infants the discounted annual medical savings could be more than $2 billion.[10]

The ultimate goal in preventing preterm birth is to eliminate the risks of neonatal complications and death.[11] Progestogen treatment with 17-OHP has been shown to prolong pregnancy for women who have had a prior preterm delivery. However, the long-term safety of this intervention is not well understood, and the legacy of diethylstilbestrol (DES) suggests caution and extended follow-up of mothers and infants. To date, 17-OHP has not shown efficacy in any population of women other than those who have had previous preterm delivery. Multiple studies in progress may help to answer these questions.

This topic area includes important components of variation in care and clinical controversy. Progesterone treatment for preventing preterm birth was first studied in several small trials during the 1960s.[12] Despite generally positive results from these trials, and positive results in subsequent larger studies, treatment with progesterone has not become widely used for the prevention of preterm delivery in women at risk.[12] In a 2005 survey, both users and non-users of 17-OHP for the prevention of preterm birth noted concerns about the need for more data on safety and efficacy and also on long-term neonatal effects, as well as about the lack of FDA approval.[9] In 2003, the American College of Obstetricians and Gynecologists stated that it is important to restrict use of 17-OHP to women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation, because unresolved issues such as optimal route of drug delivery and long-term drug safety remain.[13]

FDA Approved Treatments

No treatments approved by the Food and Drug Administration (FDA) for the prevention of preterm birth are currently on the market. A previously marketed version of hydroxyprogesterone caproate, Delalutin®, has been discontinued. Adeza submitted a new drug application to the FDA in May 2006 for Gestiva®, which is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

II. The Key Questions

Public comments included the following suggestions:

- Include all formulations of the agent in the review, including injections and compounded suppositories
- Review issues related to the accessibility of compounding pharmacies that accept insurance
- Include the correct name of the pharmaceutical agent, 17 alpha-hydroxyprogesterone caproate
- Include a comparison between non-pharmaceutical interventions, such as social support and education, and 17 alpha-hydroxyprogesterone caproate
- Examine the cost-effectiveness of the intervention

The following are responses to the public comments:

- The literature search, below, includes all formulations of progesterone, now called "progestogens" inclusively as a title/keyword search term.
- Key Questions 4 and 6 will address issues of accessibility and drug formulation.
- The official title of this project has been changed to include "Progestogens."
- All interventions compared to the use of any progestogen will be included in the review, and directly related to Key Questions 1, 4, and 5.
- De novo cost-effectiveness analyses are beyond the scope of this review. However, we will be capturing information on important health services data, including costs and any evidence of their impact on utilization as in Key Question 6.

Key Questions

Question 1

In pregnant women who are at risk for preterm birth (< 37 weeks estimated gestational age (EGA)), does progestogen treatment compared with placebo, usual care, or other interventions improve maternal or fetal/neonatal health outcomes, including but not limited to:

- Complications during pregnancy (e.g., chorioamnionitis, antenatal hospitalizations, and intrauterine growth restriction)
- Mode of birth and complications during birth (e.g., cesarean birth and surgical complications)
- Prematurity

- Postpartum and neonatal complications (e.g., maternal postpartum hemorrhage and intraventricular hemorrhage (IVH), or brain bleed)
- Longer term outcomes (e.g., neurodevelopmental delay and future reproductive outcomes)

Question 2

What is the nature and frequency of maternal and child adverse effects of progestogen treatment, including but not limited to:

- Complications during pregnancy (e.g., allergic reactions or development of gestational diabetes)
- Mode of birth and complications during birth (e.g., unanticipated maternal harms)
- Postpartum and neonatal complications (e.g., infections and sepsis)
- Longer term outcomes

Question 3

How do the effectiveness, adverse effects, and safety of progestogen treatment differ based on the maternal risk factors for preterm birth, such as severity of prior preterm birth, degree of cervical shortening, order of multiple gestations, fetal fibronectin status, preterm premature rupture of membranes (PPROM), threatened preterm birth, and socioeconomic predictors of prematurity including race/ethnicity?

Question 4

How do the effectiveness, acceptability, adherence, adverse effects, and safety of progestogen treatment differ based on the formulation, dose, frequency of administration, and gestational age (GA) at initiation or discontinuation of progestogen therapy?

Question 5

How do the effectiveness, adverse effects, and safety of progestogen treatment differ based on co-interventions used to prevent preterm birth and its consequences, including antibiotics, corticosteroids, tocolysis, and surgical interventions such as cervical cerclage?

Question 6

What is the effect of health systems and provider factors on the use of progestogens for eligible at-risk women, including provider knowledge and attitudes, provider specialty, cost of drug, availability of drug in formularies, and Medicaid and private payer coverage?

PICOTS

Population(s)

Women and subgroups of women at risk for preterm birth, including those with a prior history of preterm birth, threatened preterm birth, shortened cervical length, positive fetal fibronectin test, and multiple gestation.

Interventions

Prenatal progestogen administered in any formulation and dose, and at any frequency.

Comparators

Placebo, usual care (not including a progestogen), and other interventions to prevent preterm birth and its consequences, including antibiotics; corticosteroids; tocolysis; bedrest; dietary interventions, such as omega-3 fatty acid supplementation; surgical interventions, such as cervical cerclage; alternative modes of care, such as alternate content, conduct, and timing of antenatal visits; and non-medical interventions, such as stress reduction and social support.

Outcomes for each Key Question

Fetal/neonatal outcomes:

- Gestational age at birth, including preterm birth (< 37 weeks; cut points such as < 28, < 32, and < 34 weeks; and weeks of gestation among preterm births, as a continuous measure)
- Birthweight (mean birthweight , birthweight < 2500 grams and birthweight < 1500 grams)
- Intrauterine fetal death
- Neonatal intensive care unit (NICU) admission
- Infant hospital length of stay (LOS)
- Infant respiratory distress syndrome
- Chronic lung disease
- Need for assisted ventilation
- Need for oxygen therapy
- Intraventricular hemorrhage (IVH)
- Retinopathy of prematurity
- Necrotizing enterocolitis
- Neonatal sepsis
- Patent ductus arteriosis
- Neonatal mortality
- Neurodevelopmental delay or disability at followup
- Later childhood outcomes, such as adolescent development, or other important outcomes, including unanticipated harms

Maternal outcomes:

- Adverse effects of therapy with progestational agents (breast tenderness, nausea, headache, cough, pain, or irritation at site of administration)
- Maternal development of gestational diabetes (GDM)
- Hypertensive diseases of pregnancy

- Antenatal hospitalization
- Use of antenatal corticosteroids
- Use of antenatal tocolysis
- Use of antibiotics related to preterm birth prevention or treatment of preterm labor, threatened preterm birth, and preterm premature rupture of membranes (PPROM)
- Chorioamnionitis
- Antibiotic use during labor or after birth
- Mode of delivery
- Postpartum hemorrhage (PPH)
- Hospital length of stay
- Need for intensive care
- Death
- Measures of maternal emotional well-being, maternal preferences for treatment, adherence to treatment, and satisfaction with care or other important outcomes, including late effects of therapy remote from pregnancy

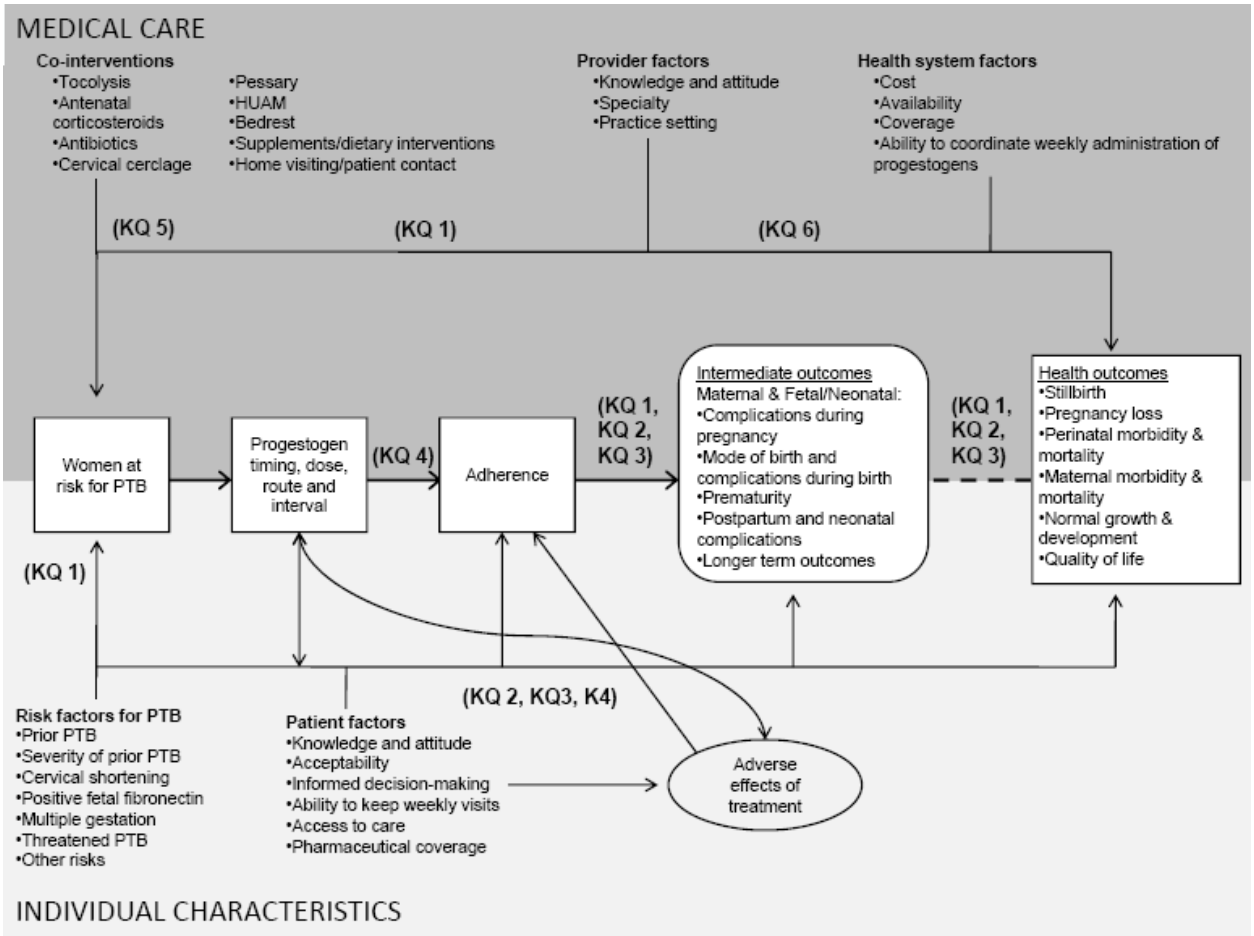
Timing

Progestogen after the first trimester through childhood.

Settings

All types of practice—for example, academic centers, public health clinics, and private practice networks—including assessment of mediating effects of health systems factors—such as provider knowledge and attitudes, specialty of care providers, availability and cost of 17-OHP, and Medicaid and private payor coverage—on the ability to provide intervention and access.

III. Analytic Framework



This figure depicts the Key Questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how the use of progestogens in women at risk for preterm birth may result in intermediate outcomes, such as complications during pregnancy (e.g., chorioamnionitis, antenatal hospitalizations, and intrauterine growth restriction), mode of birth and complications during birth (e.g., cesarean birth and surgical complications), prematurity, postpartum and neonatal complications (e.g., maternal postpartum hemorrhage and IVH), and longer term outcomes (e.g., neurodevelopmental delay and future reproductive outcomes). Adherence is influenced by the timing, dose, route, and interval of the progestogen given, patient factors such as knowledge and acceptability, risk factors for preterm birth, and adverse effects. Adverse events may occur at any point after the treatment is received, and are affected by patient factors. A woman's risk of preterm birth is determined by risk factors such as

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prior preterm birth, multiple gestations, and cervical shortening. Moreover, the timing, dose, route, and interval of the progestogen treatment may be affected by the use of cointerventions, provider factors such as specialty, and health care system factors such as cost and availability, as well as patient factors, knowledge, and attitude.

IV. Methods

We will systematically search, review, and analyze the scientific evidence for each Key Question and any related subquestions. We will look for variations in reported results for women in different age and racial or ethnic groups, as well as those with prior history/risk of preterm birth. The steps that we are taking to review the literature are described below.

We will examine existing systematic reviews and assess their quality in an effort to focus on issues related to Key Question 6 that are probably not covered in the current literature. This process will be undertaken in the following steps:

- Review of the 90 reviews found in the current search strategy
- Review of the chapter in the "Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews" regarding the use of prior reviews
- Assessment of the relevance of prior reviews in terms of PICOTS, analytic framework, and Key Questions, if they are found to be relevant as defined in the Methods Guide
- Assessment of the quality of those prior reviews using the approach described in the Methods Guide chapter (if they are of high quality, work with our experts and Task Order Office to determine whether or not to use prior reviews in place of new reviews, to abstract data from those reviews, or to update them)

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

We will review our preliminary inclusion and exclusion criteria, shown in Table 1, during the initial conference call and again during the first conference call with the Technical Expert Panel (TEP), and we will revise the criteria as appropriate. The revisions will be subject to time and budget constraints of the existing scope of work.

Table 1. Criteria for Inclusion and Exclusion of Studies in the Review

Category	Criteria
Study population	Adult females
Publication languages	English only
Admissible evidence	Study design • Controlled trials • Prospective trials with historical controls • Prospective or retrospective cohort studies • Case control studies • Medium to large case series (n > 20)

	Other criteria • Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of data and results • Abstraction of relevant outcomes from data presented in papers must be possible • Sample sizes must be appropriate for study question addressed in paper; single case reports or small case series (< 20 subjects) will be excluded

The study population will be adult females. This review will not include literature published in languages other than English. To ensure a broad literature search, no publication date limits will be used. Inclusion and exclusion criteria based on study size have not yet been finalized. The Evidence-based Practice Center (EPC) will record the size of any study that would be excluded only because it has fewer than 20 participants; the EPC will then set a study size cut-off based on the number of key or sentinel papers that would be excluded.

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

Search the Literature. We will begin with a search on topics that include various entries including, but not limited to, "preterm birth" and "preterm delivery," as well as different formulations of the intervention including "17-alpha-hydroxy-progesterone caproate," "progesterone," and "progestogen." We will search primarily MEDLINE©, but will also search EMBASE. The literature search was updated in December 2009 and in March 2010, and will be updated again in June 2010. Relevant references are being added to the pool of articles under consideration as needed, and will be added to the draft report as needed while it is being reviewed. References meeting our inclusion criteria, or of particular relevance for background sections that may be identified by public/peer reviewers, will also be incorporated.

We will use additional searches of the reference lists of existing systematic reviews or meta-analyses of progestogens for preterm birth; will also scan the and the reference lists of articles undergoing full text review will be scanned for citations which might meet inclusion criteria.

Develop Data-Collection Forms. After reviewing a sample of relevant articles, the methods lead and the content lead will design three data collection forms and test them on multiple articles; the forms will be revised as needed before each stage of data abstraction is initiated. The abstract review form will contain questions about primary inclusion and exclusion criteria. The full-text review form will be somewhat more detailed, to assist in 1) identifying studies that meet inclusion criteria and 2) conducting an initial sort of studies according to related Key Questions. The data abstraction form will be used to document those data necessary for synthesis and evidence tables; prior to data collection, we will develop and include *a priori* lists of effect modifiers (e.g., timing and route of intervention, risk factors for preterm birth, knowledge, and attitude) and expected outcomes.

Initial Review of Abstracts. We will review all titles and abstracts identified through searches against our inclusion and exclusion criteria. When differences between the reviewers arise, we will err on the side of inclusion. For studies without adequate information in the titles and abstracts to make a determination, we will retrieve full articles and review them against the inclusion and exclusion criteria.

C. Data Abstraction and Data Management

Retrieve and Review Articles. We will retrieve and review all articles meeting our predetermined inclusion and exclusion criteria or for which we have insufficient information to make a determination. The abstractor(s), the content leads and content experts, the library scientists, and the investigators will reassess each retained article against the inclusion and exclusion criteria. For the studies meeting this second-round assessment, the abstractors will extract key data elements and enter them on the data abstraction forms. Key characteristics will include but will not be limited to the following:

- Age
- Race/ethnicity
- History of preterm birth
- Risk of preterm birth—cervical shortening, positive fetal fibronectin, PPROM, multiple gestation, threatened preterm birth
- Comorbidities
- Cointerventions
- Socioeconomic status
- Maternal outcomes
- Fetal/neonatal health outcomes

For quality control, the content lead, content experts, associate director, investigators, library scientists, and/or project manager will review the data abstraction forms against the original articles. Differences will be resolved by consensus.

We will develop a simple categorization scheme for coding the reasons that articles, at the stage of full review, are not finally included in the report. The abstractor will note the reason for exclusion on the article cover page. To facilitate compilation of a list of excluded articles and codes, we will record that code in EndNote®, our bibliographic software.

Monitor Study Reviews. As reviews are conducted, the project coordinator and administrative support staff will track the status of each article. The project coordinator will maintain a master list of all retrieved articles, together with the individual assigned the initial review and abstraction review and abstraction status, review results (e.g., whether the article was selected for full review or the reason why it was not, initial review, abstraction completion date, and review by methods lead date).

The project coordinator will also monitor review progress. Weekly, the project coordinator will report on 1) the number of abstracts and articles being reviewed by the methods and content leads, and 2) the contact reviewers who determine progress, collect completed reviews, and assess completeness of each evidence table entry. Twice a month, the project staff will meet to 1) discuss the results and progress to date; 2) review cases that have been particularly difficult to classify, abstract, interpret, or adjudicate; and 3) address any review team questions. In addition, all project team members will routinely use e-mail to communicate any questions concerning the reviews.

A study characteristics spreadsheet will be developed by the project manager and project coordinator to aid the content lead, content experts, associate director, and investigators in

compiling abstracted data. These spreadsheets will facilitate counting of key data points such as study location, study type, and number of study participants.

D. Assessment of Methodological Quality of Individual Studies

To rate evidence, we expect to adapt either one of the types of grading schemes the Vanderbilt EPC has used, or one of the approaches noted as "best practices" in the EPC's review of systems. Two senior staff will separately assign quality grades; in our experience, quality grading is conducted most efficiently and consistently by senior staff. We will record quality grades in the evidence tables.

E. Data Synthesis

Prepare Evidence Tables. We will enter data from the data abstraction forms into evidence tables, using predetermined abbreviations and acronyms and otherwise attending to consistency across entries from the outset. The dimensions columns in each evidence table will vary according to Key Question, but the Tables will contain some common elements (e.g., author, publication year, study location, time period, population description, sample size, and study type). We will include information on prevalence and variation in practice. While developing the report, the content leads in consultation with epidemiologists and biostatisticians will determine the appropriateness of undertaking a meta-analysis. If a meta-analysis is not appropriate, data from the evidence tables will be synthesized and presented in summary tables in the report.

F. Grading the Evidence for Each Key Question

Quality Grading. We will develop explicit criteria for rating the overall strength of the collective evidence on each Key Question (e.g., good, fair, and poor). In so doing, we will use established concepts 1) the quantity of evidence (e.g., numbers of studies, aggregate ending sample sizes); 2) the quality of evidence (from the quality ratings on individual articles); and 3) the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge. We will make these judgments for each of the Key Questions and for any subquestions.

V. References

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VI. Definition of Terms – if applicable

None

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.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is 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. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. 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.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.