

## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Comparative Effectiveness of Treatment for Open-Angle Glaucoma

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

The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program has requested a comparative effectiveness review (CER) of glaucoma treatment. The topic was selected through the Effective Health Care Program nomination process and a review of the scientific medical literature.

##### *Description of the condition*

Glaucoma is a leading cause of visual impairment and blindness worldwide, affecting an estimated 60.5 million people.<sup>1</sup> Glaucoma is defined as an acquired disease of the optic nerve (neuropathy) that is characterized by a typically normal appearance of the optic nerve and by defects that are usually located in the mid-peripheral and nasal visual fields. Depending on whether the optic nerve damage is associated with an open or closed appearance of the channels that drain aqueous humor in the front of the eye, the glaucoma is referred to as open-angle (the subject of this report) or closed-angle.

Mild glaucoma damage to the optic nerve may be asymptomatic. As the damage worsens, however, the patient begins to have difficulty with peripheral vision, contrast sensitivity, glare, and adaptation from light to dark and dark to light—all symptoms that affect day-to-day function and quality of life. In its most severe form, glaucoma results in total, irreversible blindness.

Although the causes of glaucoma are multifactorial—and may include deficient blood supply to the optic nerve, inadequate structural support for the neurons that make up the optic nerve, and insufficient supplies of neurotrophins needed to maintain the health of the optic nerve—only elevated intraocular pressure (IOP) has been shown to be a cause of glaucoma. Both experimental models and case studies of people with unilateral glaucoma have demonstrated that elevated IOP can cause damage to the optic nerve in a pattern characteristic of glaucoma.<sup>2</sup> Furthermore, studies have demonstrated a correlation between the level of IOP and the risk of having glaucoma and of worsening glaucoma once it is present. Other studies have demonstrated that lowering IOP reduces both the incidence of glaucoma in

individuals who do not have glaucoma damage but are at high risk for its development and the rate of progression of glaucoma in individuals with established glaucoma.<sup>3-5</sup> Therefore, the treatments for glaucoma today all center around the reduction of IOP, which secondarily leads to the prevention of worsening visual field loss that can result in visual impairment and blindness.

#### *Treatments for open-angle glaucoma*

Deciding when to initiate treatment to lower IOP and what treatment modality to use to lower the IOP in a given patient is fraught with uncertainty. The types of treatment can be divided into medical, laser surgery, and incisional surgery. Medical therapy includes several classes of eye drops, such as prostaglandin analogs, beta-adrenergic antagonists, carbonic anhydrase inhibitors, alpha-adrenergic agonists, and miotics, as well as systemic carbonic anhydrase inhibitors. Laser trabeculoplasty is an office-based procedure that lowers the IOP by increasing the outflow of aqueous humor from the eye. Incisional surgery to lower the IOP comprises procedures that have been performed for decades, such as trabeculectomy and aqueous drainage device surgery, and a host of newer procedures, such as nonpenetrating deep sclerectomy, canaloplasty, endoscopic cyclophotocoagulation, and the Trabectome<sup>®</sup> system (NewMedix, Tustin, CA).

During the past 5 years there has been an increasing awareness of the barriers involved in the medical treatment of glaucoma in terms of the ability of patients to initiate and persist in the correct use of IOP-lowering eye drops.<sup>6</sup> Any study of the effectiveness of glaucoma treatment must take this adherence and persistence with medical therapy into account.

#### *Rationale for a comparative effectiveness review*

Although there are important clinical trials that have compared medical and laser therapies with observation only in patients with early glaucoma, initial medical therapy with initial surgical therapy in patients with established glaucoma, and laser therapy with surgical therapy in patients whose glaucoma is not controlled with medical therapy, trials are single randomized controlled trials and in most cases do not include newer medical and surgical treatments.<sup>5,7,8</sup>

In conclusion, there have been developments in the treatment of glaucoma since the last systematic reviews were completed, including the realization of the importance of adherence to medical therapy

and the introduction of new surgical modalities. For this reason, it is appropriate to update and possibly revise statements about the appropriateness of glaucoma treatment.

### *Objectives*

The objective of this review is to summarize the evidence regarding the safety and efficacy of medical, laser, and other surgical treatments for open-angle glaucoma with a specific focus on the effects of treatment on visual impairment, patient-reported outcomes, intraocular pressure, visual field loss, optic nerve damage, and harms and adverse effects.

A detailed description of Food and Drug Administration (FDA) approval status, indications, and warnings for each of the medications and devices considered for this review is presented in Appendix A.

## **II. The Key Questions**

### **Summary of Revisions to the Key Questions**

Based on the public comments regarding the Key Questions submitted to AHRQ, the Evidence-Based Practice Center (EPC) revised the Key Questions and protocol by:

1. Limiting the definition of visual impairment to the definition included in the International Classification of Diseases, 9th Revision, Clinical Modification<sup>9</sup> (hereafter, ICD-9-CM). (Key Question 1)
2. Clarifying that vision-related quality of life includes vision-related functional loss and the impact of functional loss on activities of daily living. (Key Question 2)
3. Including treatment convenience as a patient-reported outcome. (Key Question 2)

The EPC identified an error in the original wording of Key Question 5, so it was revised to reflect the proposal to examine the relationship of intermediate and final health outcomes as illustrated in the analytic framework (Section III).

### **Key Questions**

*Source:* [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

*Published Online:* November 16, 2010

- Key Question 1. Do medical, laser, and other surgical treatments for open-angle glaucoma reduce visual impairment?
- Key Question 2. Does treatment of open-angle glaucoma improve patient-reported outcomes?
- Key Question 3. Do medical, laser, and other surgical treatments for open-angle glaucoma lower intraocular pressure (IOP)?
- Key Question 4. Do medical, laser, and other surgical treatments for open-angle glaucoma prevent or slow the progression of optic nerve damage and visual field loss?
- Key Question 5. Does lowering intraocular pressure or preventing or slowing the progression of optic nerve damage and visual field loss reduce visual impairment and change vision-related quality of life?
- Key Question 6. What are the harms associated with medical, laser, and other surgical treatments for open-angle glaucoma?

### Populations

We will include studies of participants with primary or secondary chronic open-angle glaucoma or open-angle glaucoma suspects aged 40 years and older. These types of glaucoma may also be described in the literature as the following conditions:

- Ocular hypertension
- Low-tension glaucoma
- Pseudoexfoliative glaucoma/pseudoexfoliation syndrome
- Pigmentary glaucoma
- Steroid-responsive glaucoma

There will be no limitations based on stage or severity of disease, disease etiology, comorbid ocular or other medical conditions, geographic location, or demographic characteristics (e.g., gender, race/ethnicity).

## Interventions

We will include studies of medical treatments (eye drops and systemic treatment), laser surgery, and incisional surgery for open-angle glaucoma.

### *Medical treatments*

Studies of the following agents (alone or in any possible combination) will be considered for this review: prostaglandin analogs,  $\beta$ -adrenergic antagonists, topical and oral carbonic anhydrase inhibitors,  $\alpha_2$ -adrenergic agonists, and parasympathomimetics. Preparations of the above-mentioned agents by their trade and generic/chemical names are included in Appendix B.

### *Laser and incisional surgical treatments*

Studies of the following surgical treatments and the use of devices that are designed to increase aqueous outflow will be considered for this review:

### Office-based laser treatments

- Argon and selective laser trabeculoplasty

### Surgical procedures

- Trabeculectomy
- Aqueous drainage devices
  - Baerveldt<sup>®</sup> implant (Advanced Medical Optics, Inc., Santa Ana, CA)
  - Ahmed<sup>®</sup> implant (New World Medical, Inc., Rancho Cocamonga, CA)
  - Krupin implant (E. Benson Hood Lab, Inc., Pembroke, MA)
  - Molteno<sup>®</sup> implant (Molteno Ophthalmic Limited, Dunedin, New Zealand)
- Cyclophotocoagulation, both transscleral and endoscopic

- Deep sclerectomy
- Visco canalostomy

### Specialized Surgical Devices

- iScience microcatheter (canaloplasty; iScience Interventional, Menlo Park, CA)
- Trabectome<sup>®</sup> System (modified trabeculotomy; NewMedix, Tustin, CA)
- ExPRESS shunt (modified trabeculectomy; Optonol Ltd., Neve Ilan, Israel)
- Glaukos iStent<sup>™</sup> (trabecular bypass; Glaukos Corporation, Laguna Hills, CA)
- SOLX<sup>®</sup> Gold Shunt (trabecular bypass; SOLX, Inc., Medway, MA)

### Comparators

Key Questions 1, 2, 3, 4, and 6 explore comparisons of medical treatments, laser surgery, and incisional surgery for open-angle glaucoma to each other (e.g., medical vs. laser, medical vs. medical) or to no treatment. For Key Questions 1, 2, 3, 4, and 6 we will also include studies in which the intervention is laser or incisional surgery for glaucoma but the comparator is a combined or staged procedure for cataract and glaucoma (e.g., surgical treatments for glaucoma combined or staged with phacoemulsification or extracapsular cataract extraction).

### Outcomes

1. Outcomes for Key Question 1:
  - a. *Primary outcome:* The proportion of participants with moderate, severe, and profound visual impairment (as defined in the ICD-9-CM<sup>9</sup>). We will also consider other measurements of visual impairment as defined by included studies.
  - b. *Secondary outcome:* We will also compare visual acuity outcomes (as measured by the Early Treatment Diabetic Retinopathy Study [ETDRS] or the Snellen Eye Test) among the treatment groups of interest as reported in included studies (e.g., mean visual acuity or proportion of participants in pre-specified visual acuity categories).
2. Outcomes for Key Question 2:

Mean total or relevant item/subscale scores of the participants as measured by any validated questionnaire—for example, the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ)—for the following patient-reported outcomes will be compared among the treatment groups of interest:

a. *Primary outcome:*

(1). Vision-related quality of life, that is, vision-related functional loss as well as the impact of functional loss on activities of daily living.

b. *Secondary outcomes:*

(1). Treatment convenience

(2). Patient satisfaction

(3). Patient preference values or utility values

(4). Adherence to medical treatment

3. Outcomes for Key Question 3: The proportion of participants with intraocular pressure measurements at prespecified levels as outlined below will be compared among the treatment groups of interest (primary outcomes). Since the analysis of intraocular pressure may vary appreciably by trial, we will consider other intraocular pressure outcomes as reported in included studies.

a. An intraocular pressure of  $\leq 18$  mm Hg

b. A decrease in intraocular pressure of  $\geq 20$  percent from baseline levels

4. Outcomes for Key Question 4:

a. The proportion of participants with progressive optic nerve damage as defined by included studies and as observed via fundus photography or other imaging of the posterior pole.

b. The proportion of participants with progression of visual field loss as defined by the Early Manifest Glaucoma Trial<sup>10</sup> and as measured by automated threshold perimetry. We will also consider other assessments of visual field loss as defined by included studies.

5. Outcomes for Key Question 6:

The proportion of participants experiencing the following adverse events will be compared among the treatment groups of interest:

1. Cataract formation (visually significant cataract requiring surgery or report of cataract surgery)
2. Low intraocular pressure (hypotony)
3. Decreased visual acuity
4. Infection (e.g., blebitis, endophthalmitis)
5. Inflammation
6. Strabismus
7. Ocular surface disease
8. Retinal tear and detachment
9. Patient discomfort
10. Skin discoloration
11. Conjunctival injection
12. Iris color change
13. Punctal stenosis
14. Conjunctival foreshortening
15. Peripheral anterior synechiae
16. Systemic allergic reaction
17. Cardiac arrhythmia
18. Respiratory problems
19. Death

### **Description of Key Question 5**

Key Question 5 explores the association of 1) lowering intraocular pressure or 2) preventing or slowing the progression of a) optic nerve damage and b) visual field loss (intermediate outcomes of treatment) and final health outcomes (reduced visual impairment and improved vision-related quality of life) among the populations of interest. The outcomes are as described above in *Outcomes* for Key Questions 1 through 4, and the criteria for inclusion/exclusion are described in Section IV-A.

### **Timing**

Outcomes will be assessed at 1 year of follow-up and at annual intervals thereafter.

### **Settings**

Eye care provider (ophthalmologists and optometrists) clinical settings.

### III. Analytic Framework

**Figure 1. Analytic Framework for Treatment of Open-Angle Glaucoma**

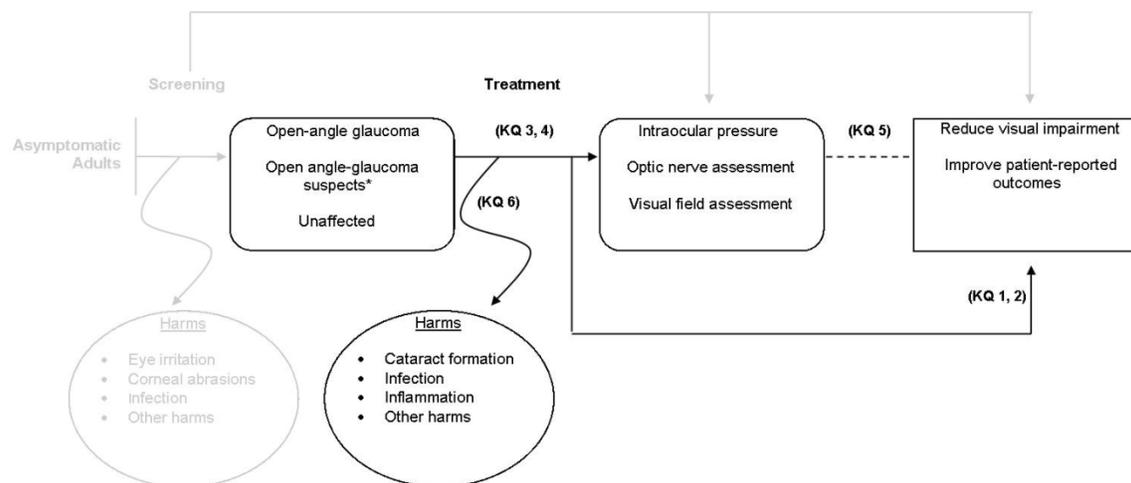


Figure 1: The above figure is a modified version of a larger framework depicting the impact of both screening and treatment for open-angle glaucoma. This figure focuses on the treatment portion of the framework and depicts the key questions (KQs) within the context of the inclusion criteria described in the previous sections. In general, the figure illustrates how treatment of open-angle glaucoma may reduce visual impairment (KQ 1) and/or improve patient-reported outcomes (KQ2). It shows how treatment of open-angle glaucoma may reduce intraocular pressure (KQ3) and/or prevent or slow the progression of optic nerve damage and visual field loss (KQ4). The framework also illustrates that there

may be a relationship between intermediate and final health outcomes (KQ5). Finally, the potential harms of treatment (KQ6) are illustrated in the framework.

## **IV. Methods**

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

For Key Questions 1 through 4, we will include randomized controlled trials (RCTs) and quasi-randomized controlled trials of medical treatments and laser, and incisional surgery for open-angle glaucoma. Observational study designs, to include cohort and case control studies in addition to randomized controlled trials, will be considered for Key Questions 5 and 6. Narrative summaries of case reports and case series (including more than 100 participants) will also be presented for Key Question 6. The specific populations, interventions, and outcomes of interest are described in Section II.

### **B. Searching for the Evidence: Literature Search Strategies for Identifying Relevant Studies**

We will search the following databases for primary studies: MEDLINE, EMBASE, LILACS (Latin American and Caribbean Literature on Health Sciences), and CENTRAL (the Cochrane Central Register of Controlled Trials). We will develop a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori and adapt this search strategy for searches of EMBASE (using Emtree terms) and CENTRAL.

We will search the literature without imposed language, sample size, or date restrictions.

We will search reference lists of included studies, relevant review articles, and related systematic reviews to identify any additional studies for inclusion. We will also use the Science Citation Index-Expanded database to identify additional studies that may have cited trials included in this review. Conference proceedings or journals will not be hand searched.

In addition, we will review the Scientific Information Packets provided by the manufacturers of the glaucoma medications and devices. We will also explore pharmaceutical medication registries.

The MEDLINE search strategy to be used is:

("Ocular Hypertension"[mh] OR "ocular hypertension"[tiab] OR "Intraocular Pressure"[mh] OR "intraocular pressure"[tiab] OR "Low Tension Glaucoma"[mh] OR glaucoma[mh] OR glaucoma[tiab]) AND ("Trabeculectomy"[mh] OR trabeculectomy[tiab] OR "Laser Coagulation"[mh] OR "laser coagulation"[tiab] OR photocoagulation[tiab] OR "sclerostomy"[mh] OR sclerostomy[tiab] OR canaloplasty [tiab] OR viscocanalostomy[tiab] OR "glaucoma drainage implants"[mh] OR "glaucoma drainage implants"[tiab] OR shunt[tiab] OR "laser therapy"[tiab] OR "laser surgery"[tiab] OR apraclonidine[tiab] OR "brimonidine"[Substance Name] OR brimonidine[tiab] OR "Timolol"[mh] OR Timolol[tiab] OR "Betaxolol"[Mesh] OR Betaxolol [tiab] OR "Levobunolol"[mh] OR "Metipranolol"[mh] OR "Carbonic Anhydrase Inhibitors"[mh] OR "Carbonic Anhydrase Inhibitors"[tiab] OR "dorzolamide"[Substance Name] OR dorzolamide[tiab] OR "Acetazolamide"[mh] OR Acetazolamide[tiab] OR "Cholinergic Agents"[mh] OR "Pilocarpine"[mh] OR Pilocarpine[tiab] OR "Carbachol"[mh] OR "Prostaglandins, Synthetic"[mh] OR Prostaglandins[tiab] OR travoprost[tiab] OR bimatoprost[tiab] OR latanoprost[tiab] OR "isopropyl unoprostone"[Substance Name] OR "Antihypertensive Agents"[mh] OR "Epinephrine"[mh] OR Epinephrine[tiab]) NOT (animals [mh] NOT humans [mh])

We will search LILACS by using the terms glaucoma\$ AND (a list of medical and surgical treatments as outlined in the MEDLINE search). The list will be linked by the Boolean operator "OR" and will contain the truncation symbol "\$" to capture words with the same root.

Primary authors of included studies will be contacted to provide missing information regarding study methodology, missing standard deviations, intention to treat data, or other data as appropriate. If no response is received within 6 weeks, we will assess the study based upon the available data provided in the published article.

### **C. Data Abstraction and Data Management**

Potentially relevant citations will be screened by using DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), a Web-based systematic review software. Citations identified by the search strategies will be uploaded to DistillerSR and managed in the following manner: Two reviewers will independently

assess titles and abstracts resulting from the literature searches according to the inclusion criteria stated in Section IV-B. The titles and abstracts will be classified as “include,” “exclude,” or “unsure.”

Disagreements regarding eligibility are identified by DistillerSR and will be resolved by discussion with each reviewer by providing a rationale based on the review of titles, abstracts, and/or full text articles. The two reviewers will retrieve the full text for titles and abstracts classified as “unsure” by both reviewers or classified as “unsure” by one reviewer and “include” by a second reviewer and reassess the studies for inclusion. The authors of studies classified as “unsure” will be contacted for further clarification, as appropriate, after examining the full text according to the guidelines described in Section IV-A. Any disagreements regarding inclusion after full text review will be resolved through discussion, and unresolved conflicts will be adjudicated during a team meeting of investigators and advisors. Studies labeled as “exclude” by both review authors will be excluded from the review and the reasons for exclusion documented. Studies labeled “include” will be further assessed for methodological quality as described in Section IV-D.

Two reviewers will extract descriptions of the study methods to include the population, intervention(s), and outcomes of interest by using a form designed by the team investigators, advisors, and senior research methodologist. Disagreements will be resolved through discussion. Data will be entered independently by two reviewers into a database designed specifically for this CER.

#### **D. Assessment of Methodological Quality of Individual Studies**

We will use the Cochrane Collaboration’s tool for assessing the risk of bias of randomized and quasi randomized trials. Two authors will independently assess the included studies for sources of systematic bias according to the guidelines in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*<sup>11</sup> and will evaluate the studies for the following criteria: sequence generation and allocation concealment (selection bias), masking of participants, study investigators, and outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Masking of investigators and participants might not be possible with some of the interventions being examined, but it will be noted when mentioned.

Judgments for each criterion will be reported as “Yes” (low risk of bias), “No” (high risk of bias), or “Unclear” (information is insufficient to assess). Two reviewers will resolve disagreements through discussion. We will contact the authors of the studies for additional information on issues that were unclear from information available in the original reports. In case of failure to communicate with the primary investigators, or if there is no response within 6 weeks, we will assess the methodological quality on the basis of the available information.

We will use the Newcastle-Ottawa Scale (NOS)<sup>12</sup> for assessing the methodological quality of observational studies to include cohort and case control studies. The NOS includes domains to assess the quality of *study group selection* (representativeness, case definitions), *comparability of cohorts/cases and controls on the basis of design or analysis*, and *ascertainment of exposure(s) or outcome(s)*. One star is awarded for the four selection questions and three stars for the ascertainment of exposure/outcome questions. Up to two stars are awarded for the comparability domain.

## E. Data Synthesis

If there is appreciable variability in the studies with regard to interventions, follow-up intervals, or assessments of outcomes, we will not combine the results in a meta-analysis and will instead present a narrative summary.

### Assessments of heterogeneity

We will assess the clinical, methodological, and statistical heterogeneity of included studies. We will evaluate clinical and methodological heterogeneity by examining potential variations in participant characteristics, inclusion/exclusion criteria, and assessments of primary and secondary outcomes. The  $I^2$  statistic (%), the Chi-square test for heterogeneity, and the degree of overlap in confidence intervals of the included studies will be examined to assess statistical heterogeneity.

### Assessment of reporting biases

A funnel plot will be used to assess reporting biases in conjunction with study characteristics or other factors that may contribute to asymmetry of the plot.

## Measures of treatment effect

We will calculate summary risk ratios or odds ratios as appropriate for dichotomous outcomes. We will verify the normality of continuous outcomes and calculate mean differences. Standardized mean differences will be calculated if continuous outcomes are measured by using different scales.

## Data synthesis

If the  $I^2$  statistic suggests considerable heterogeneity (a threshold will be established before undertaking any analyses) or if there are insufficient data (less than three studies), we will not combine the results in a meta-analysis and will instead present a narrative summary. If considerable heterogeneity does not exist based on the  $I^2$  statistic and an inspection of the forest plot, we will combine the results of included trials in a meta-analysis by using fixed or random effects methods as appropriate.

## Subgroup analysis

If there are sufficient data, we will conduct subgroup analyses by stage or severity of disease, by relevant demographic characteristics (e.g., age, race/ethnicity), and by other factors as outlined in *Populations*. We will also conduct a subgroup analysis of studies in which the intervention is laser surgery or incisional surgery for glaucoma but the comparator is a combined or staged procedure for cataract and glaucoma.

## F. Grading the Evidence for Each Key Question

We will assess the quantity, quality, and consistency of the body of available evidence addressing Key Questions 1 through 6. We will use an evidence grading scheme recommended by the GRADE Working Group,<sup>13</sup> adapted by AHRQ in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,<sup>14</sup> and recently published in the *Journal of Clinical Epidemiology*.<sup>15</sup>

We will consider the strength of the study designs; randomized controlled trials will be graded as having the highest level of evidence followed by the observational studies. and observational studies as having the lowest. If an outcome is evaluated by at least one randomized controlled trial and by observational studies, our evidence grade will be based firstly on the randomized controlled trials and secondly on the

quality of the cohort studies. If an outcome is evaluated by one or no randomized controlled trials, our evidence grade will be based on the single randomized controlled trial and the best available observational study.

We will assess the quality and consistency of the best available evidence, including assessment of the risk of bias in relevant studies, as well as aspects of consistency, directness, and precision as described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*<sup>14</sup> and by Owens and colleagues.<sup>15</sup> For each outcome of interest, two reviewers will grade the major outcomes for each Key Question and then the entire team will discuss their recommendations and reach consensus.

## V. References

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## VI. Definition of Terms

Definitions and abbreviations are listed in Appendix C.

## VII. Summary of Protocol Amendments

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

## VIII. Review of Key Questions

For CERs, the key questions are posted for public comment and finalized after the comments are reviewed. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the Evidence-based Practice Center (EPC) and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is to be reviewed.

## IX. Technical Expert Panel (TEP)

The TEP is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived to be healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, study designs, 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 perform analyses of any kind nor does it 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 reviewers may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. For some specific reports, such as reports requested by the Office of Medical Applications of Research at the 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. 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 3 months after the publication of the evidence report.

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