

Evidence-based Practice Center Systematic Review Protocol

Project Title: *Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension – An Update of the 2007 Report*

I. Background and Objectives for the Systematic Review

More than 65 million American adults – approximately one-third – have hypertension. The prevalence of hypertension increases with advancing age. More than half of individuals 60-69 years of age and approximately three-quarters of individuals 70 years of age and older have hypertension.¹ In addition to being the number one attributable risk factor for death throughout the world,² hypertension results in substantial morbidity because of its impact on numerous target organs, including the brain, eyes, heart, arteries, and kidneys.

Despite the high morbidity and mortality attributable to hypertension, control remains suboptimal. In addition to several effective nonpharmacological interventions – including diet, exercise, and control of body weight – many individuals will require antihypertensive medication to lower blood pressure.

Among the many choices in antihypertensive therapy, some of the most common are those aimed at affecting the renin-angiotensin-aldosterone (renin) system. The renin system is an important mediator of blood volume, arterial pressure, and cardiac and vascular function. Components of this system can be identified in many tissues. The primary site of renin release is the kidney. The system can be triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Via proteolytic cleavage, renin converts the decapeptide substrate angiotensinogen I to the octapeptide angiotensin II. Angiotensin II acts directly on the resistance vessels to increase systemic vascular resistance and arterial pressure; stimulates the adrenal cortex to release aldosterone leading to increased sodium and water reabsorption and potassium excretion; promotes secretion of antidiuretic hormone leading to fluid retention; stimulates thirst; promotes adrenergic function; and increases cardiac and vascular hypertrophy.

Therapies aimed at modifying the renin system have been used extensively for treatment of hypertension, heart failure, myocardial infarction, diabetes, and renal disease. Currently, three classes of therapy that interact with this system are used to inhibit the effects of angiotensin II: 1) angiotensin converting enzyme inhibitors (ACEIs); 2) angiotensin II receptor antagonists (ARBs or angiotensin receptor blockers); and 3) direct renin inhibitors. ACEIs block conversion of angiotensin I to angiotensin II. ARBs selectively inhibit angiotensin II from activating the angiotensin specific receptor (AT₁). Direct renin inhibitors block the conversion of angiotensinogen to angiotensin I.

Although ACEIs and ARBs both target the renin system and are treated equivalently by clinicians, this may not be appropriate. While they both reduce the downstream effects of angiotensin II, it is not clear that these medications are in fact clinically equivalent. ACEIs, for example, do not entirely block production of angiotensin II due to the presence of unaffected converting enzymes. Also, ACEIs have well known side effects not shared by ARBs, including cough (estimated incidence 5% - 20%) and angioedema (estimated incidence 0.1% to 0.2%, with

a lesser reported risk with ARBs).³ Additional considerations arise with the newer direct renin inhibitors because their side-effect profiles and efficacy may be more favorable than either ACEIs or ARBs. Given the public health importance and widespread use of these agents, it is important to understand their comparative effects on clinical outcomes.

In this comparative effectiveness review, we will update the 2007 report on “Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension.” Similar to the earlier review, we will examine the scientific literature of ACEIs (Table 1) and ARBs (Table 2) for individuals with hypertension. In this update also, we will evaluate the use of direct renin-inhibitors for the treatment of hypertension (Table 3). The outcomes analyzed in this comparison will include relative benefits (blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes) and safety (adverse events, tolerability, persistence, and adherence). In addition, we will examine the clinical determinants of these outcomes by sex, comorbidities, concurrent medication use, race/ethnicity, and age. The focus will be on long-term outcomes.

Table 1. List of angiotensin converting enzyme inhibitors (ACEIs), with the U.S. Food and Drug Administration (FDA) approval status and examples of significant warnings.

Generic Name	US Trade Name	FDA Approval	Warnings – Increased Risk
Benazepril	Lotensin [®]	June 1991	Hypotension Syncope Headache Dizziness Fatigue Rash/hypersensitivity Hyperuricemia/gout Diarrhea Renal insufficiency Hyperkalemia Cough Angioedema
Captopril	Capoten [®]	1981	
Enalapril/ Enalaprilat	Vasotec [®]	Dec. 1985	
Fosinopril	Monopril [®]	May 1991	
Lisinopril	Prinivil [®] , Zestril [®]	Dec. 1987	
Moexipril	Univasc [®]	April 1995	
Perindopril	Aceon [®]	Dec. 1993, not available until mid-1999	
Quinapril	Accupril [®]	Nov. 1991	
Ramipril	Altace [®]	Jan. 1991	
Trandolapril	Mavik [®]	May 1996	

Table 2. List of angiotensin II receptor antagonists (ARBs), with FDA approval status and examples of significant warnings.

Generic Name	US Trade Name	FDA Approval	Warnings – Increased Risk
Candesartan Cilexetil	Atacand [®]	June 1998	Hypotension Syncope
Eprosartan	Teveten [®]	Dec. 1997, not	

		available until 1999	Hyperkalemia Renal insufficiency
Irbesartan	Avapro [®]	Sept. 1997	
Losartan	Cozaar [®]	April 1995	
Olmesartan Medoxomil	Benicar [®]	April 2002	
Telmisartan	Micardis [®]	Nov. 1998	
Valsartan	Diovan [®]	Dec. 1996	

Table 3. List of non-peptide, orally-active direct renin inhibitors, with FDA approval status and examples of significant warnings.

Generic Name	US Trade Name	FDA Approval	Warnings – Increased Risk
Aliskiren	Tekturna [®]	March 2007	Hypotension, rash, hyperkalemia, diarrhea, elevated creatine kinase, renal insufficiency, cough, angioedema

II. The Key Questions

Question 1: For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?

Question 2: For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence, and adherence?

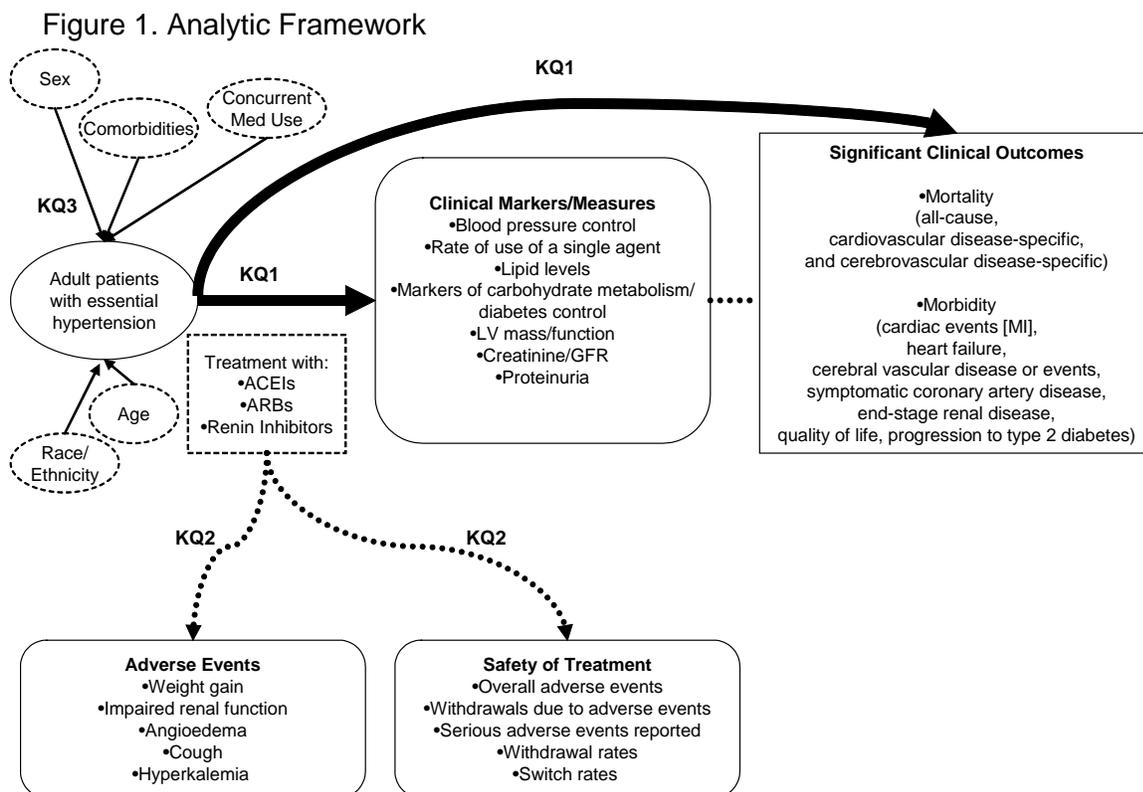
Question 3: Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs, ARBs, or direct renin inhibitors are more effective, associated with fewer adverse events, or better tolerated?

- **Population(s):**
 - We will include adult patients (age 18 year or older) with essential hypertension, as defined by study authors. We will include studies with patients of mixed ages and mixed diagnoses only if results were reported separately for the relevant subgroups. Specific patient subgroups evaluated will be stratified by sex, comorbidities, concurrent medication use, race/ethnicity, and age.
- **Interventions and Comparators of Interest:**
 - The interventions include the medications listed in Tables 1-3.
 - Specifically this includes:

- ACEIs:
 - benazepril (Lotensin®), captopril (Capoten®), enalapril/enalaprilat (Vasotec®), fosinopril (Monopril®), lisinopril (Prinivil®, Zestril®), moexipril (Univasc®), perindopril (Aceon®), quinapril (Accupril®), ramipril (Altace®), and trandolapril (Mavik®)
- ARBs
 - candesartan (Atacand®), eprosartan (Teveten®), irbesartan (Avapro®), losartan (Cozaar®), olmesartan (Benicar®), telmisartan (Micardis®), and valsartan (Diovan®)
- Direct renin inhibitors
 - aliskiren (Tekturna®)
- In addition to straightforward comparisons of a single ACEI versus a single ARB or a single direct renin inhibitor, we will also include “grouped” comparisons (e.g., a specific ARB versus “ACEIs” or unspecified “ARBs” versus unspecified “ACEIs”) and comparisons of an ACEI + drug X versus an ARB + drug X (e.g., losartan + hydrochlorothiazide [HCTZ] versus enalapril + HCTZ).
- We will exclude comparisons of an ACEI + drug X versus an ARB + drug Y (e.g., enalapril + mandipine vs. irbesartan + HCTZ).
- Studies with treatment protocols that permitted the addition of other antihypertensive medications during the trial if certain blood pressure targets were not met will be included provided the cointervention protocols were the same in both groups.
- **Outcomes**
 - Primary Outcomes
 - Blood pressure control (we will prefer seated trough blood pressure, where reported)
 - Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific)
 - Morbidity (especially major cardiovascular events [myocardial infarction , stroke] and measures of quality of life)
 - Safety (focusing on serious adverse event rates, overall adverse event rates, and withdrawals due to adverse events, withdrawal rates, switch rates)
 - Specific adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, hyperkalemia)
 - Persistence/adherence
 - Rate of use of a single antihypertensive for blood pressure control
 - Secondary Outcomes:
 - Lipid levels (high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol [TC], and triglyceride [TG])

- Rates of progression to type 2 diabetes
 - Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], insulin or other diabetes medication dosage, fasting plasma glucose, or aggregated measures of serial glucose measurements).
 - Measures of LV mass/function (left ventricular mass index [LVMI] and ejection fraction [LVEF])
 - Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria)
- **Timing:**
 - We are focusing on *long-term* benefits and harms of ACEIs versus ARBs versus direct renin inhibitors for treating essential hypertension and interpret this based on our previous report to be 12 weeks or longer.
 - **Settings:**
 - We do not restrict the setting of the included studies in our analysis

III. Analytic Framework



Alternate Text: This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how ACEIs, ARBs, and direct renin inhibitors may result in clinical markers or measures such as blood pressure control, lipid

levels, markers of carbohydrate metabolism/diabetes control, measures of LV mass/function, or measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria) and/or clinically significant outcomes such as mortality (all cause, cardiovascular disease-specific, and cerebrovascular disease-specific) or morbidity (especially major cardiovascular events [MI, stroke], rates of progression to type 2 diabetes, and measures of quality of life). Also, adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, hyperkalemia) may occur at any point after the treatment is received.

IV. Methods

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

We will use the same inclusion/exclusion criteria as in our original report with some small modifications described below

Abstract Screening Instructions

An abstract will be **included** if all of the following criteria apply:

- The study is a direct comparison (any study design) of an ACEI versus an ARB, or an ACEI versus a renin inhibitor, or an ARB versus a renin inhibitor (see Tables 1-3 for included drugs; additional antihypertensive therapy acceptable if the same in both groups);
- Original data.

An abstract will be **excluded** if any of the following criteria apply:

- No patients have hypertension OR some patients have hypertension, but results not reported separately for this subgroup;
- All subjects aged < 18 years OR some subjects aged < 18 years, but results not broken down by age;
- Only comparison is an ACEI + an ARB versus placebo.

An abstract will be identified as a **review** if it is a relevant review article, meta-analysis, methods article, or cost-effectiveness analysis.

For each abstract, please mark either “EX” for **Exclude**, “IN” for **Include** or “Rev” for **Review**.

For included studies, please mark:

- “AcVAr” if the study is a direct comparison of an ACEI versus an ARB;
- “AcVR” if the study is a direct comparison of an ACEI versus a direct renin inhibitor
- “ArVR” if the study is a direct comparison of an ARB versus a direct renin inhibitor

For all included studies, please also indicate the longest length (weeks or months) of followup.

Thus, coding for each abstract should be either:



- **EX**
- **Rev**
- **IN AcVAr** (specify # weeks or # months follow-up, or write “NS” if length of follow-up not specified)
- **IN AcVR** (specify # weeks or # months follow-up, or write “NS” if length of follow-up not specified)
- **IN ArVR** (specify # weeks or # months follow-up, or write “NS” if length of follow-up not specified)
- **Info** (if full-text needed to assess eligibility)

ACEIs vs. ARBs vs Direct Renin Inhibitor Comparisons – Full-Text Screening Criteria

1) Condition of interest = essential hypertension

- **Exclude** if no patients have essential hypertension *or* if results not reported separately for subgroup with essential hypertension

2) Population of interest = adults (≥ 18 years)

- **Exclude** if all subjects < 18 *or* if results not reported separately for ≥ 18 subgroup

3) Interventions & comparators of interest:

ACEIs, ARBs, and direct renin inhibitors listed in Tables 1-3

- **Include** “grouped” comparisons, e.g., specific ARB vs. “ACE inhibitors” or unspecified “ARBs” vs. unspecified “ACEIs”
- **Include** ACEI + drug X vs. ARB + drug X (e.g., losartan + HCTZ vs. enalapril + HCTZ)
- **Exclude** ACEI + drug X vs. ARB + drug Y (e.g., enalapril + manidipine vs. irbesartan + HCTZ)
- **Exclude** if ACEI, ARB, or direct renin inhibitor not on above list

4) Study designs:

- **Include** all clinical study designs (RCTs, non-RCTs, cohorts, etc.); cross-sectional studies acceptable if time on treatment reported and ≥ 12 weeks
- **Exclude** if not clinical study (review, etc. – please specify)

5) Outcomes of interest:

For Key Questions 1 and 3:

- Intermediate outcomes:
 - Blood pressure control
 - Rate of use of a single antihypertensive agent for blood pressure control
 - Lipid levels
 - Progression to type 2 diabetes
 - Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, aggregated measures of serial glucose measurements)

- LV mass/function
- Creatinine/GFR
- Proteinuria
- Health outcomes:
 - Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific)
 - Morbidity (cardiac events [MI], heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end-stage renal disease, peripheral vascular disease [as clinically manifest, not markers of], quality of life)

For Key Questions 2 and 3:

- Safety (overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, switch rates)
- Specific adverse events, including but not limited to weight gain, impaired renal function, angioedema, cough, hyperkalemia
- Tolerability
- Persistence
- Adherence

6) Sample size:

- We will not exclude articles based on sample size during the full text screening but may re-visit this decision when performing the full-text abstraction and synthesis.

7) Treatment duration/length of followup:

- **Exclude** if treatment duration or longest followup < 12 weeks

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

Our search strategy will use the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE[®] and adapted for use in other databases. We will search MEDLINE[®] (May 2006 to present) and the Cochrane Central Register of Controlled Trials (current issue, 2009). Our inclusion of direct renin inhibitors will not be limited by publication date.

In addition, we will receive scientific information packets from the Scientific Resource Center and will explore www.clinicaltrials.gov for additional trials.

All citations will be imported into an electronic database (EndNote X3).

We will include English-language reports of controlled trials or cohort studies that compared an angiotensin II receptor antagonist (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan) with an angiotensin-converting enzyme inhibitor (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, andtrandolapril) in patients with essential hypertension, and reported an included outcome. Additionally, for this review update, we will be including the information that has recently been

acquired using a direct renin-inhibitor (aliskiren). Aliskiren is currently the only medication in this classification being used to treat patients with hypertension. (See Appendix A for the current search strategy and initial number of abstracts to be included in our abstract screening stage of this updated report.)

C. Data Abstraction and Data Management

Globally, the research team will update data abstraction forms/evidence table templates used in the original report for abstracting data for the key questions. A sample data abstraction form and additional guidance on assessing quality and applicability from our original is provided in Appendix B and will be adapted for this update. Based on clinical expertise, a pair of researchers will be assigned to the research questions to abstract data from the eligible articles. One of the pair will abstract the data, and the second researcher will over-read the article and the accompanying abstraction to check for accuracy and completeness.

Specifically for this project, the data abstraction forms will include data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographics and data needed for determining outcomes (intermediate outcomes, health outcomes, and safety outcomes). The safety outcomes will be framed to help identify angioedema and hyperkalemia, which are both adverse events (AEs) of particular interest in evaluating these classes of hypertension medication.

D. Assessment of Methodological Quality of Individual Studies

The included studies will be assessed on the basis of the quality of their reporting of relevant data. We will evaluate the quality of individual studies using the approach described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. To assess quality, we will employ the strategy to: (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. To evaluate methodological quality, we will apply criteria for each study type derived from core elements described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,⁴ *Rating the Strength of Scientific Evidence: Relevance for Quality Improvement Programs*,⁵ and *Systems to Rate the Strength of Scientific Evidence*.⁶ To indicate the summary judgment of the quality of the individual studies, we will use the summary ratings of good, fair, and poor.

To assess applicability, we will use the PICOTS format to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*.⁴

E. Data Synthesis

We will summarize the primary literature by abstracting relevant continuous and categorical data. We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the results reported.



F. Grading the Evidence for Each Key Question

The strength of evidence for each key question will be assessed using the approach described in the *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*.⁴ The evidence will be evaluated using the four required domains: risk of bias, consistency, directness, and precision. Additionally, when appropriate, the studies will be evaluated for: coherence, dose-response association, residual confounding, strength of association (magnitude of effect), publication bias, and applicability. The strength of evidence will also be assigned an overall strength of evidence grade of high, moderate, low, or insufficient.

V. References

1. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 1995;25:305-13.
2. World Health Organization. World health report 2002: reducing risks, promoting healthy life. World Health Organization. Geneva, Switzerland. Available at: www.who.int/whr/2002. Accessed December 14, 2006.
3. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Ann Intern Med* 1992;117:234-42.
4. Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. Version 1.0 [Draft posted Oct. 2007]. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf. Accessed December 4, 2009.
5. Lohr KN. Rating the strength of scientific evidence: relevance for quality improvement programs. *Int J Qual Health Care* 2004;16:9-18.
6. West S, King V, Carey T, et al. Systems to Rate the Strength of Scientific Evidence. Evidence Report/Technology Assessment No. 47 (Prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center under Contract No. 290-97-0011). AHRQ Publication No. 02-E016. Rockville, MD: Agency for Healthcare Research and Quality. April 2002. Available at: <http://www.ncbi.nih.gov/bookshelf/br.fcgi?book=hserta&part=A73054>. Accessed December 4, 2009.

VI. Definition of Terms – if applicable

ACEIs	Angiotensin converting enzyme inhibitors
AEs	Adverse events
AHRQ	Agency for Healthcare Research and Quality
ARBs	Angiotensin II receptor antagonists
AT ₁	Angiotensin specific receptor



CERs	Comparative Effectiveness Reviews
EPC	Evidence-based Practice Center
FDA	U. S. Food and Drug Administration
GFR	Glomerular filtration rate
HbA1c	Glycated hemoglobin
HCTZ	Hydrochlorothiazide
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVMi	Left ventricular mass index
Med	Medication
MeSH	Medical Subject Headings
MI	Myocardial infarction
NIH	National Institutes of Health
OMAR	Office of Medical Applications of Research
PICOTS	<u>P</u>opulation, <u>I</u>nterventions, <u>C</u>omparators of interest, <u>O</u>utcomes, <u>T</u>iming, and <u>S</u>ettings
PVD	Peripheral vascular disease
RCT	Randomized control trial
TC	Total cholesterol
TEP	Technical Expert Panel
TG	Triglyceride

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 (*Standard Language*)

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 (OMAR), National Institutes of Health (NIH) 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.