Evidence-based Practice Center Systematic Review Protocol

Project Title: ***The title should succinctly indicate the interventions or exposures, and the associated health or social problem addressed in the review. Indicate that this is a systematic review.***

Initial publication date if applicable:

Amendment Date(s) if applicable:

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Describe topic background, including details about the condition (epidemiology, etiology, burden of disease, etc.), decisional dilemmas, current relevant practices, or other information to provide context for the systematic review. Define relevant populations or contextual factors related to the scope of the review. Define the intervention and its components if relevant. Include information on the FDA status, indications, and warnings for use of any drugs or devices covered in the systematic review; if extensive, include in an appendix. Describe the rationale for the systematic review and what it would add to the body of literature already available on the topic.

Do not name the nominator or partner unless express permission was obtained.

II. The Key Questions

Introduction: Summarize the public comments regarding the key questions (if applicable). Describe major changes made since the key questions were posted for comment, with rationale for making (or not making) changes. Include dates of public posting.

Identify for each key question – preferred format includes both inclusion and exclusion criteria:

- **Population(s):**
  - Condition(s), disease severity and stage, comorbidities, patient demographics.
- **Interventions:**
  - List medications by generic name, with class of drug and other relevant details. For devices, list type with relevant key features or characteristics. Include dosage, frequency, and methods of administration. If extensive may include this information as a table or as an appendix
  - For tests (e.g. diagnostic, prognostic), define whether test is a triage test, replacement test, or an add-on test.
  - For bundled interventions, define the components of the intervention.
  - Include description of co-interventions, if any.
- **Comparators:**
  - Specify whether placebo, usual care, or active comparators, including

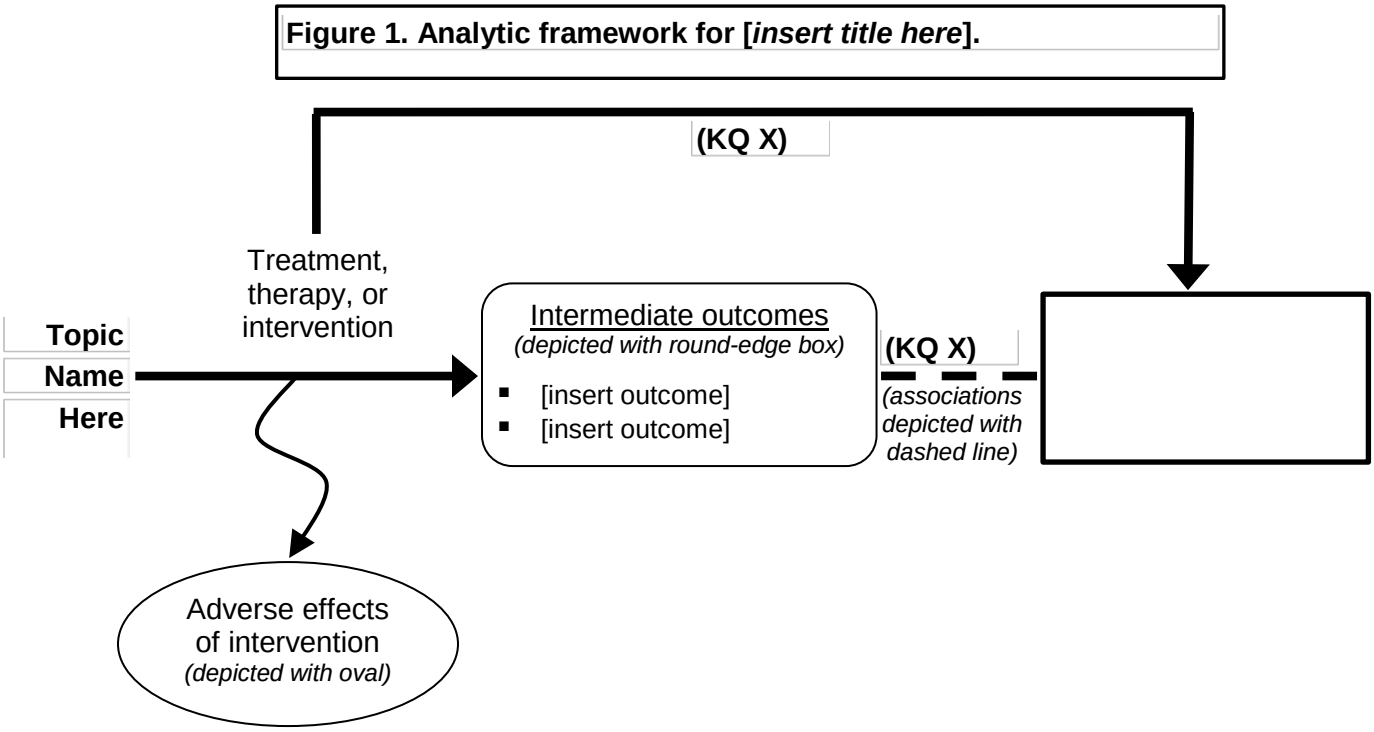
other treatments or tests.

- **Outcomes:**
  - Clearly defined final health outcomes (clinical and patient-centered outcomes). Prioritize when possible (e.g., primary and secondary).
  - Clearly defined intermediate outcomes
  - Adverse effects (outcomes), including those related to the included intervention(s)
  - Note which outcomes will have strength of evidence grading.
  - Indicate validated instruments and scales if possible, for outcome assessment.
  - If a primary outcome determines the inclusion criteria be aware of the risk of selective outcome bias by excluding studies because outcomes are not reported.
- **Timing:**
  - Duration of follow-up
  - Timing of intervention, frequency of intervention, if relevant and known.
- **Settings:**
  - Clearly defined settings (For example primary care, outpatient, specialty, in-patient, acute care setting, long term care setting, etc.

III. Analytic Framework

Provide an analytic framework to illustrate the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis. Details of the analytic framework should be consistent with the KQ and PICOTS.

Analytic Framework



Include alternate text to accompany the figure (for 508 compliance) **in a separate file**.

For example:

Figure 1: This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how [treatment 1] versus [treatment 2] may result in intermediate outcomes such as A, B or C and/or final health outcomes such as X, Y or Z. Also, adverse events may occur at any point after the treatment is received.

IV. Methods

Reference the Methods Guide where relevant, and note any modifications to Evidence-based Practice Center (EPC) Program methods. Whenever possible cite the JCE papers for the methods chapters. Summarize rather than provide extensive detail, with a goal of 10 pages. Use future tense, even if some steps are partially completed.

Criteria for Inclusion/Exclusion of Studies in the Review - Include the inclusion/exclusion criteria by target population, interventions, outcomes, setting, study characteristics. Include the rationale for decisions regarding study design, language restrictions, study size, study quality, publication date range, and any potentially controversial decisions. Endorsement by technical experts or key informants is not considered sufficient justification.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions - Provide the full proposed electronic search strategy (i.e. such that search could be repeated) for at least one database (may refer to the appendix), what two or more databases (e.g. PubMed, EMBASE, PsychInfo, other content specific databases) will be searched, why they were selected, and dates of coverage for the electronic searches. Include specific plans for updating the literature search during the project (e.g. during peer review of the draft report). Indicate who will peer review the main electronic search strategies and what instrument will be used for review. Describe how hand searches may be done.

Provide a description of the proposed search strategy for grey literature including sources (e.g. conference abstracts, clinicaltrial.gov, National Guidelines Clearinghouse, grey literature databases) and rationale. Do not include results. Include specific plans for updating the grey literature search (e.g. during peer review of the draft report).

Please indicate that a Supplemental Evidence And Data for Systematic review (SEADS) portal will be available and whether or not a Federal Register Notice will be posted for this review.

Describe the process for selecting studies (e.g. title/abstract and full text review) against the inclusion/exclusion criteria, and for resolution of disputes. Include any mechanisms that are in place to ensure quality control. Note details such as number of reviewers, activities, and specific roles.

Describe process for evaluating the appropriateness and incorporating additional data identified through public and peer review; from the grey literature search; or from scientific information packets.

Report the reasons why study authors would be contacted for additional data.

Data Abstraction and Data Management - Describe how the data are abstracted from each study and methods for collecting and managing the information. Describe what mechanisms are in place to ensure quality control (e.g. data abstraction templates may be included as an Appendix, use of dual independent abstraction, linking studies to avoid duplication).

List and define data items that will be extracted (e.g. PICOS, funding source, risk of bias factors, effect modifiers). Identify key characteristics that might be necessary for evidence synthesis due to their role in effect modification of the intervention-

treatment association and thus limit the applicability of findings. For example, in a review of bisphosphonates for osteoporosis, it would be important to abstract data on gender, calcium intake, exercise, age, weight, etc. Describe any anticipated data assumptions and simplifications.

Assessment of Methodological Risk of Bias of Individual Studies - Discuss criteria for assessing risk of bias (ROB) or quality of studies meeting inclusion criteria. Describe any unique aspects of the specific specialty literature and/or specific study design elements that may need to be taken into consideration in the ROB assessment. Include a reference or description of a validated tool for each study design assessed (including systematic reviews if relevant), if used. If the tool is adapted provide rationale. A copy of the entire tool is not necessary. Define summary terminology for any categorization of ROB of individual studies that will be used. Describe methods for assessing overall ROB (or quality) assessment from individual criteria and methods for resolving disagreements. Note whether assessments will be done at individual study outcome level or overall study level.

Data Synthesis - Discuss how evidence will be summarized (e.g. quantitatively or qualitatively) in a clinically relevant manner. Describe how ROB assessment and study design, including systematic reviews, will be used in synthesis. Describe methods for determining under what conditions a meta-analysis will be considered, and if conducted, sufficient details as to how it will be done. Describe any plans to conduct analysis of indirect comparisons if interventions have not been compared directly in included studies (e.g. network meta-analysis).

Describe any planned outcome summary measures (e.g. major adverse cardiac events).

Clearly state methods for exploring statistical heterogeneity (e.g. sensitivity analysis or meta-regression), and pre-define clinical groups that are too heterogeneous to allow for meta-analysis or clinical groups for which the qualitative analysis will be presented separately. Identify a priori subgroups that will be explored to explain potential heterogeneity.

If the EPC investigators plan to exclude studies from meta-analysis at this stage (e.g. high ROB studies) provide rationale and note that sensitivity analysis will be done.

Describe how the authors will present findings in the report, such as the ordering of outcomes or other categorization scheme.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

Describe the process for grading the strength of evidence (SOE) for major comparisons and outcomes. Include any mechanisms that are in place to ensure quality control. Details include number of reviewers, roles, and method for resolving disagreement.

Describe methods for selecting the major outcomes for strength of evidence grading (i.e. did key informants or TEP help inform prioritization of outcomes). List the specific outcomes that will be graded (if not already indicated in the PICOTS) and provide rationale for selection.

Describe and define what domains will be used to determine overall strength of the body of evidence for each key question. Describe how SOE domains will be combined to determine overall strength of evidence. Define minimum important difference if used. Note any deviations from the EPC methods guide and rationale.

Describe how individual study (or individual study outcome) ROB assessments and study designs will be combined into an overall study limitations domain in the SOE grading. Also when quantitative synthesis is precluded describe how domains of directness, precision, consistency, and reporting bias will be assessed.

Assessing Applicability – Describe *a priori* factors (e.g. population, interventions, settings, etc.) that may limit the applicability of findings. Define the clinical or patient subgroup factors that may cause or explain heterogeneity of treatment effect.

V. References

VI. Definition of Terms

If not applicable, simply make a note to that effect.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale

This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.

(NOTE THE FOLLOWING PROTOCOL ELEMENTS ARE STANDARD SECTIONS TO BE ADDED TO ALL PROTOCOLS)

VIII. Review of Key Questions

Delete this section if no topic refinement.

The Agency for Healthcare Research and Quality (AHRQ) posted the key questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Delete this section if no topic refinement.

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 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 AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

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

XIII. Role of the Funder

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

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).