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:

Amendment Date(s) if applicable:

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

The background should articulate the decisional dilemmas and logic and lead to a clear understanding of why the **specific** questions of the systematic review should be addressed. This information should encompass the purpose and the target audience for the review. (See example in box below.)

Within the framework of the decisional dilemmas, describe current relevant practices and other relevant context for the scope and purpose of the systematic review, including populations. The EPC should include the following issues when they bear on an understanding of the decisional dilemmas, the context of these dilemmas, and the purpose of the review:

- Discuss any standards, variations, or uncertainty about disease diagnosis.
- Be specific about the interventions and pertinent comparisons of interest and those that may require separate consideration due to heterogeneity of treatment effect.
- Describe particular issues for complex interventions, such as individual component parts, groupings of intervention classes, or theoretical basis, as appropriate.
- Include contextual information on existing standards or guidelines, availability, use, and practice. Think explicitly about the setting in which decisions are being made.
- Include relevant FDA status, indications, and warnings for use of any drugs or devices covered in the systematic review; if extensive, summarize in the main document (perhaps with a table) and include details in an appendix.

Do not name the nominator or partner unless you have obtained their express permission.

Example: Background and Scope

Project Title: Acute Pain Management by Emergency Medical Services in the Prehospital Setting.

Background

Appropriate management of acute trauma pain is an integral part of patient management in the prehospital setting. Prevalence of pain varies in this setting; estimates range from 20% to 53%. Although adequate pain relief minimizes anxiety and cardiac complications associated with acute pain, as many as 43% of individuals have insufficient prehospital pain relief. Reasons for this include fear of adverse events with analgesic administration, unwanted masking of underlying pathology, and provider indifference to pain complaints. Under-treatment of pain in the prehospital setting paired with the recent focus on reducing opioid exposure creates a need for clinicians to have a thorough understanding of pain assessment tools and the comparative effectiveness and safety of analgesics for prehospital acute pain management.

For patients experiencing moderate to severe pain, current guidelines strongly recommend (based on moderate quality evidence) initial management with a weight-based opioid, either intravenous (IV) morphine or IV/intranasal fentanyl. However, the epidemic of opioid abuse in the United States, combined with concerns of adverse events—such as vomiting and subsequent airway obstruction, respiratory depression, hypotension, and sedation—has caused policy makers and providers to seek alternatives. These include ketamine, nitrous oxide/oxygen, acetaminophen, and non-steroidal anti-inflammatory drugs. Although a variety of non-pharmacologic modalities are also available (e.g., splinting or distraction), our review will not include them.

In addition to the effectiveness and harms of prehospital analgesia, we will also examine issues pertaining to emergency medical services (EMS) personnel who administer pain treatment. This group could include physicians, mobile intensive care units, helicopter teams, and military medical professionals. Potential issues include differential effectiveness of prehospital analgesia based on administering EMS provider as well as potential direct harms to the providers themselves.

Purpose of the Review

This systematic review will assess the comparative effectiveness and harms of opioid and non-opioid analgesics for the prehospital management of acute pain to support a revision of the current guidelines. The intended audience includes guideline developers, health system administrators, and the EMS personnel who administer prehospital pain relief medications.

II. Key Questions

Introduction: Summarize the public comments regarding the Key Questions (if applicable). Describe major changes made as the result of public comment. Include dates of public posting. Consider that scope and key question formation may differ for complex interventions.[1]

Identify the population, interventions, comparators, outcomes, timing, and settings (PICOTS) for each key question as they pertain to the decisional dilemmas – preferred format includes both inclusion and exclusion criteria:

- **Population(s):**
  - Condition(s), disease severity and stage, comorbidities, and patient demographics, including important subgroups.
- **Interventions:**
  - List medications by generic name, with class of drug and other relevant details. Describe nonpharmacologic interventions. For devices, list type with relevant key features or characteristics.
    Include dosage, frequency, and methods of administration. If this information is extensive, include it 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.[2]
  - For bundled interventions, define the components of the intervention.
  - Describe co-interventions, if any.
- **Comparators:**
  - Specify whether these are placebo, usual care, wait list, or active comparators, including other treatments or tests.
- **Outcomes:**
  - Clearly define final health (clinical and patient-centered) outcomes. *Consider conducting a formal or semi-structured outcome prioritization process with Key Informants (KI) and members of the Technical Expert Panel (TEP). This should include the partner perspective.*
  - Specify primary and secondary outcomes of interest—including harms
  - List potential serious adverse effects (outcomes), including intervention- related adverse or side effects.
  - Clearly define intermediate outcomes, if relevant.
  - Specify which outcomes which the EPC will grade for strength of evidence.[3]
  - If instruments or scales have been validated for outcome assessment, identify them.
  - *If a primary outcome determines the inclusion criteria, be aware of the risk of selective outcome bias if you exclude studies that do not report on that outcome.*

[1] Butler, Mary et al. AHRQ series on complex intervention systematic reviews—paper 3: adapting frameworks to develop protocols, Journal of Clinical Epidemiology , Volume 90 , 19 - 27
[2] Bossuyt, P.M., et al., Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ, 2006. 332(7549): p. 1089-92.
[3] G.H. Guyatt et al., GRADE guidelines: 2. Framing the question and deciding on important outcomes Journal of Clinical Epidemiology 64 (2011) 395-400

- **Timing:**
  - Indicate duration of follow-up
  - If relevant and known, list the timing and frequency of intervention.
- **Settings:**
  - Clearly define settings (e.g., primary care, outpatient, specialty, inpatient, acute care, long-term care).

Example: Key Questions

Project Title: Acute Pain Management by Emergency Medical Services in the Prehospital Setting.

KQ 1: What is the comparative effectiveness of the initial analgesic agent treatment for achieving reduction in moderate-to-severe acute-onset pain level when administered by EMS personnel in the prehospital setting?

KQ1a. How does effectiveness vary by patient characteristics?

KQ1b. How does effectiveness vary by routes of administration, dosing, and timing?

KQ 2: What is the comparative effectiveness of analgesic agents for decreasing the memory of pain and painful events for patients with moderate-to-severe pain in the prehospital setting?

KQ 3: What are the comparative harms of analgesic agents when administered by EMS personnel to control moderate-to-severe pain in the prehospital setting?

KQ3a. How do harms vary by patient characteristics?

KQ3b. How do harms vary by routes of administration, dosing, and timing?

KQ3c. What are the comparative harms to EMS personnel who administer analgesics to patients for the control moderate-to-severe pain in the prehospital setting?

KQ 4: In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what is the comparative effectiveness of switching to another analgesic agent compared with repeating the initial treatment?

KQ4a. How does effectiveness vary by patient characteristics?

KQ4b. How does effectiveness vary by timing of the second treatment administration?

KQ 5: In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what are the comparative harms of switching to another analgesic agent?

KQ5a. How do harms vary by patient characteristics?

KQ5b. How do harms vary by routes of administration, dosing, and timing?

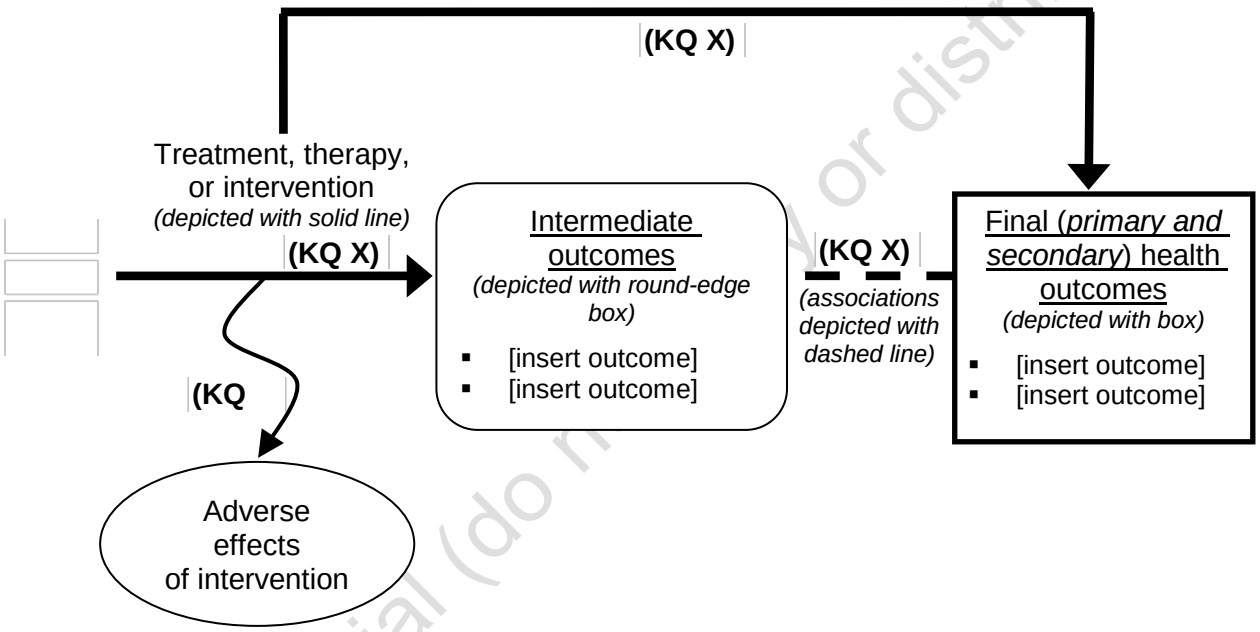
KQ 6: What is the comparative accuracy of pain assessment tools in the prehospital setting for special populations?

Contextual Question: Which treatments are contraindicated for specific medical conditions or patient characteristics (e.g., dental pain, abdominal pain, depressed blood pressure, heart rate, and/or respiratory rate, altered mental status, agitation)?

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 KQs and PICOTS. Also consider that details of the analytic framework may differ for complex interventions.[4]

Figure 1. Analytic framework for [*insert title here*].



Include alternate text to 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 below. 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 patients receive the treatment.

IV. Methods

Reference the Methods Guide[5] where relevant and note any modifications to Evidence-based Practice Center (EPC) Program methods. Whenever possible, cite the JCE papers for the methods chapters.

[4] Butler, Mary et al. AHRQ series on complex intervention systematic reviews—paper 3: adapting frameworks to develop protocols, Journal of Clinical Epidemiology , Volume 90 , 19 - 27
[5] https://epc-src.ahrq.gov/src/secureEHC/content.cfm?AREA=1&FLDR=3576

Summarize rather than provide extensive detail, with a goal of 10 pages for this section. 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 populations, interventions, outcomes, timeframes, settings, and study characteristics. Include the rationale for decisions regarding inclusion or exclusion criteria related to study design, language, geographic location, study size, study quality, publication date range, and any potentially controversial decisions. Justification for inclusion or exclusion must include more than technical expert or key informant recommendation.

Literature Search Strategies To Identify Relevant Studies to Answer the Key Questions: Provide the full proposed electronic search strategy (i.e., such that the search could be repeated) for at least one database (may refer to the appendix), what other (two or more) databases (e.g., MEDLINE, EMBASE, PsychInfo, or other content-specific databases) will be searched, 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 if the main electronic search strategies will be peer reviewed and what instrument will be used for review. Describe how hand searches may be done.

Describe the proposed search strategy for gray literature including sources (e.g., conference abstracts, clinicaltrial.gov, gray literature databases) and rationale. Do not include results. Include specific plans for updating the gray literature search (e.g., during peer review of the draft report).

Indicate that a Supplemental Evidence And Data for Systematic review (SEADS) portal will be available and whether 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 of incorporating additional data identified through public and peer review, from the gray literature search, or from SEADS packets.

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

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

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

association. For example, in a review of bisphosphonates for osteoporosis, the EPC would identify factors such as age, sex, calcium intake, exercise, and weight. Describe any anticipated data assumptions and simplifications, and discuss how these might limit applicability of findings.

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 literature and study design elements that the EPC may need to consider in the ROB assessment. Describe the key ROB domains to be evaluated for each study design assessed (including those for systematic reviews, if relevant). If using an existing ROB tool, provide a reference and note any adaptations you will make (with justifications for those changes). A copy of the entire tool is not necessary. Define summary terminology (e.g., high, moderate, and low) for any categorization of ROB of individual studies that the EPC will use. Describe methods for assessing overall ROB (or quality) from individual criteria and methods for resolving disagreements. Note whether assessments will be done at the individual study outcome level or at the overall study level; if the latter, justify this choice.

Data Synthesis: Describe how the EPC will summarize evidence -- e.g., quantitatively or qualitatively, or both -- in a clinically relevant or actionable manner. Describe how the EPC will use ROB assessment and study design in this synthesis. Also describe how data from previous systematic reviews will be used.

Describe methods for determining under what conditions the EPC will consider doing one or more meta-analysis; if any meta-analyses are likely to be conducted, give sufficient details as to how the EPC will carry them out. 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). Define clinical groups that are likely to be 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 and important differences in benefits or harms.

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 analyses will be done.

Describe how the EPC will present findings in the report, such as methods for determining summary statements (including how to consider the magnitude and direction of effect size, significance, consistency, and study limitations.), 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. List

all outcomes that the EPC will grade and provide rationale for selection[6]; limit these to the outcomes most important to the decisional dilemmas.

Describe methods for selecting the outcomes for grading (e.g., note whether KI or TEP members helped establish any priorities for selecting these outcomes). Include any mechanisms the EPC has to ensure quality control. Details include number of reviewers, roles, and methods for resolving disagreement.

Define a threshold, minimally important difference, or minimal clinically important difference that the EPC will use to reach a conclusion of "no difference." Define any other thresholds that will be used in drawing conclusions from the evidence.

Describe how the EPC will assess domains for each Key Question. Describe how the EPC will combine domains to determine overall strength of evidence.

Assessing Applicability: Identify the factors (e.g., population, interventions, settings) for which there may be sufficient heterogeneity of treatment effect and thus conclusions from one group may not be applicable for another group.

V. References

VI. Definition of Terms

Define terms unlikely to be universally understood by an audience of health care professionals, including medical or clinical terms, analytic terms, and any acronyms or abbreviations. If the protocol contains no terms that need definition, make a note to that effect.

VII. Summary of Protocol Amendments

If the EPC needs to amend the protocol, it should give the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol. Table 1 below illustrates the format:

[6] G.H. Guyatt et al., GRADE guidelines: 2. Framing the question and deciding on important outcomes Journal of Clinical Epidemiology 64 (2011) 395-400

Table 1. Summary of Protocol Amendments

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 language in the revised protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use as justification "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 TEXT TO BE ADDED TO ALL PROTOCOLS, except where noted.)

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 them after reviewing of the public comments and seeking 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; they can include 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 the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the 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. They do not review 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. The Technical Expert Panel is 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 fosters 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; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP 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 preparing 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 3 months after 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 with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can 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. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

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 the EPC response to 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 either 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).