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Evidence-based Practice Center Systematic Review Protocol

Project Title: *Pharmacologic Management of Acute Pain by EMS in the Prehospital Setting*

Initial publication date: October 30, 2018

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I. Background and Objectives for the Systematic Review

Appropriate management of acute pain is an integral part of patient management in the prehospital setting. The prevalence of pain specifically in the prehospital setting varies, with estimates ranging from 20-53%.¹ Adequate pain relief is known to minimize the anxiety and cardiac complications associated with acute pain.² However, as many as 43% of individuals have insufficient prehospital pain relief.³ Reasons for this have included fear of adverse events with analgesic administration, unwanted masking of underlying pathology, and provider indifference to pain complaints, amongst others.⁴⁻⁶ Under-treatment of pain in the prehospital setting paired with the recent focus on optimizing 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.

Since pain cannot be adequately treated if it is not appropriately assessed, a careful evaluation of validated tools to measure pain in the prehospital setting is required. Current guidelines⁷ for the management of prehospital trauma pain recommend specific pain scales, broken into age-related categories. However, a known limitation to this literature base is the dearth of studies comparing the diagnostic accuracy of pain assessment tools in the prehospital setting particularly in the absence of a gold standard assessment tool.⁸ Of particular interest is the evidence for use of these scales in special populations including pediatrics, those with cognitive impairment, substance impairment, and non-English speakers.

Management of Acute Pain in the Prehospital Setting

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 (IN) fentanyl.⁷ Complicating the appropriate use of prehospital opioids is the fear of their abuse and the resulting epidemic in the United States.^{9,10} When combined with concerns of adverse events, such as vomiting and subsequent airway obstruction, respiratory depression, hypotension, and sedation,¹¹ alternative analgesics have been sought. Non-opioid analgesics, including ketamine, nitrous oxide/oxygen, acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDs) are of particular interest. A variety of non-pharmacologic modalities are also available (e.g. splinting, distraction, etc.), although they are not included in the current review.

In addition to the effectiveness and harms of prehospital analgesia, issues pertaining to emergency medical services (EMS) personnel who administer the drugs are of interest. This group could include physicians,¹² mobile intensive care units,¹³ helicopter teams,^{14,15} and military medical professionals. Potential issues include direct harms of prehospital analgesia to the EMS provider themselves.

Impetus for 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.

II. The Key Questions

The scope and key questions (KQs) for this topic were developed by the Agency for Healthcare Research and Quality (AHRQ) in conjunction with the National Highway Traffic Safety Administration (NHTSA) and UConn Evidence-based Practice Center (EPC).

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

KQ2a. How do harms vary by patient characteristics?

KQ2b. How do harms vary by routes of administration, dosing, and timing?

KQ2c. 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 3: In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what is the comparative effectiveness of switching the analgesic regimen compared to repeating the initial treatment?

KQ3a. How does effectiveness vary by patient characteristics?

KQ3b. How does effectiveness vary by timing of the second treatment administration?

KQ 4: 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?

KQ4a. How do harms vary by patient characteristics?

KQ4b. How do harms vary by routes of administration, dosing, and timing?

Contextual Question 1: 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)?

Contextual Question 2: What is the evidence regarding use of pain assessment tools in the prehospital setting for special populations including children, individuals with cognitive impairment, substance impaired individuals, and non-English speakers?

For the KQs the following PICOTS criteria apply:

Population(s):

- KQ 1-4:
 - Patients of any age with acute onset pain, categorized as traumatic or non-traumatic pain. Pain associated with labor and delivery will be excluded.
 - Moderate or severe pain will be determined by the study itself and we will not exclude based on the specific tool or threshold used by the study to define moderate or severe pain.
 - Studies that target mild pain or non-zero pain to administer analgesics will be excluded.
- KQ 3 and 4:
 - In addition to what is specified above, patients must be considered inadequately responsive to the first analgesic. The definition of “inadequate response” will be based on what is used in the study. We will not exclude based on the threshold or tool used by the study to determine adequacy of response.
- Sub-KQa
 - Sub-KQa targets population characteristics that may be potential modifiers of the original KQ.
 - KQ1a, 2a, 3a, 4a: Age, source of pain, severity of pain, medical condition (including chronic pain, chronically painful conditions or chronic opioid users), location of the pain, and vital signs.
 - KQ2c: EMS personnel that administer or handle analgesics in the care of patients with acute onset, non-traumatic, moderate to severe pain. EMS personnel who administer or handle analgesics include emergency medical technicians, advanced emergency medical technicians, and paramedics.

Interventions:

- KQ 1-4:
 - Opioids (morphine, fentanyl) or non-opioids (ketamine, nitrous oxide/oxygen, NSAIDs [ketorolac, ibuprofen] acetaminophen) or the combination of ketamine with either morphine or fentanyl; regardless of dose, frequency or route of administration (oral, subcutaneous, intravenous, intramuscular, intraosseous, intranasal, inhaled, transdermal).
 - We will exclude other interventions that are not listed such as nonpharmacologic treatments, placebo, no treatment, other combinations of interventions or complimentary alternative medicine.
- KQ 3 and 4:

- Administration of the initial drug at a different dose than the initial dose or administration of a different analgesic. Analgesics include opioids (morphine or fentanyl), ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac, ibuprofen), acetaminophen, or the combination of ketamine with either morphine or fentanyl.
- Sub-KQb:
 - Sub-KQb targets characteristics of the analgesic regimen or training and background of the personnel that may be potential modifiers of the original KQ.
 - 1b, 2b: route of administration, dose of analgesic and frequency of dose, EMS personnel training/background.
 - 3b, 4b: timing of the second analgesic, EMS personnel training/background.

Comparators:

- KQ 1-4:
 - Opioids (fentanyl or morphine), ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac, ibuprofen), acetaminophen or the combination of ketamine with either morphine or fentanyl; regardless of dose, frequency or route of administration (oral, subcutaneous, intravenous, intramuscular, intraosseous, intranasal, inhaled, transdermal).
 - We will exclude other interventions that are not listed such as nonpharmacologic treatments, placebo, no treatment, and other combinations of interventions or complimentary alternative medicine.
- KQ 3 and 4:
 - The initial analgesic regimen (i.e. repeat the same drug and dose) studied which the patient was determined to be inadequately responsive to.

Outcomes:

- KQ 1,3:
 - Pain severity scores and presence of pain, as defined by the tools and thresholds used in the included studies; time to analgesic effect; dissociative experiences scale responses; self-reported recall of pain episode
- KQ2, 4:
 - Heart rate, respiratory rate, respiratory depression, hypotension, nausea, vomiting, mental status changes, emergence delirium, any adverse event (as in any subject that experienced an adverse event during the study period)
- KQ2c:
 - Needle sticks, future risk of substance abuse or misuse, diversion

Timing:

- There are no restrictions based on timing.

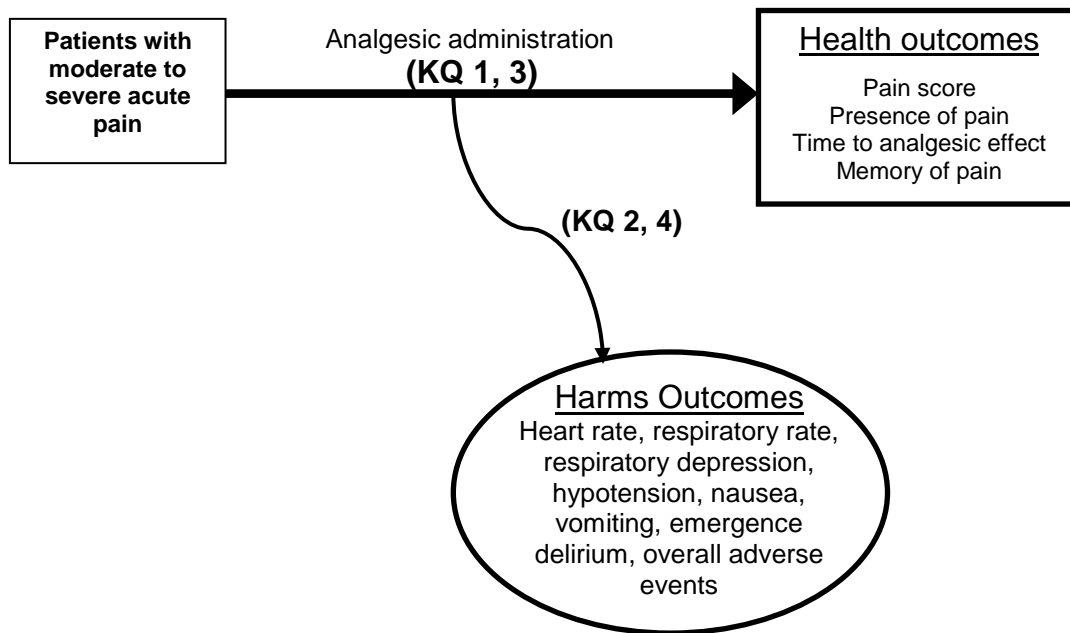
Settings:

- The primary setting of interest is prehospital. Based on preliminary literature searches, there may be some KQs where literature is scant or non-existent in the prehospital setting. In such cases we will consider the battlefield settings and/or the emergency department setting where patients are treated by emergency department personnel.

Study Designs

- Randomized controlled trials, case-controlled, cohort studies.

III. Analytic Framework



IV. Methods

KEY QUESTIONS

The methods for this comparative effectiveness review follow the guidance provided in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for the EPC program.¹⁶

Criteria for Inclusion/Exclusion of Studies in the Review- Inclusion and exclusion criteria for the KQs are listed in Table 1, consistent with the PICOTS above.

Table 1. Inclusion and exclusion criteria for KQs

Category	Inclusion Criteria	Exclusion Criteria
Population	KQ 1-4: Any age with acute onset, moderate to severe pain. Pain will be categorized as traumatic or non-traumatic. KQ3 and 4: Above plus considered inadequately responsive to the initial analgesic.	KQ 1-4: Pain associated with labor and delivery; mild or non-zero pain severity
Intervention	KQ 1-4: Opioids (morphine or fentanyl), ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac or ibuprofen), acetaminophen, ketamine combined with either morphine or fentanyl; regardless of dose, frequency or route of administration KQ 3 and 4: The analgesic must vary in dose or drug, from the initial analgesic the patient was determined inadequately responsive to. Analgesics include opioids (morphine or fentanyl), ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac or ibuprofen), acetaminophen, ketamine combined with either morphine or fentanyl.	KQ 1-4: Any other combination or single interventions such as other analgesics, nonpharmacological, placebo, no treatment or complimentary alternative medicine. KQ 3 and 4: Administration of the same drug and dose as the initial analgesic, which the patient was determined to be inadequately responsive to.
Comparator	KQ 1-4: Opioids (fentanyl or morphine), ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac, ibuprofen), acetaminophen, ketamine combined with either morphine or fentanyl; regardless of dose, frequency or route of administration KQ 3 and 4: The initial analgesic regimen studied that the patient was determined to be inadequately responsive to.	KQ 1-4: Any other single interventions such as other analgesics, nonpharmacological, placebo, no treatment or complimentary alternative medicine. Any combinations of treatments that are not specified in the inclusion criteria. KQ 3 and 4: Comparisons to analgesic regimens other than the initial regimen the patient was determined to be inadequately responsive to.
Outcomes	KQ 1 and 3: Pain severity scores, presence of pain, time to analgesic effect, dissociative experiences scale, self-recall of pain episode KQ 2 and 4: Heart rate, respiratory rate, respiratory depression, hypotension, nausea, vomiting, emergence of delirium, total adverse events ^a KQ2c: needle sticks, future risk of substance abuse or misuse, diversion	Studies that do not include at least one of the outcomes listed in the PICOTS
Timing	All study durations and follow-ups will be included	None
Setting	Prehospital. If needed we will first consider battlefield settings or emergency department settings.	All other settings.
Study Design	RCTs, nonrandomized controlled trials, prospective or retrospective controlled cohort studies, case-controlled studies	Case series, case reports, studies without an active comparator or non-active control group
Publication Language and Dates	No limits on publication date or language ^b	Abstracts without published study manuscripts.

Abbreviations: KQ=key question; NSAIDs=nonsteroidal anti-inflammatory drugs; PICOTS=population, intervention, comparator, outcomes, timing, setting; RCT=randomized controlled trial

^a: Total adverse events as in the total number of subjects that experienced an adverse event

^b: English language abstracts of non-English language articles will be reviewed at the abstract stage consistent with the process described by the Methods Guide.¹⁶

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions – One search will be implemented for the KQs1-4. Appendix A shows the preliminary search strategy formatted for MEDLINE that are comprised of medical subject heading (MeSH) terms and natural language terms reflective of the population and interventions. The search strategy will be adapted for the other databases as needed. We will conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. We will investigate any literature that the peer reviewers or the public suggest and, if appropriate, will incorporate additional studies into the final review. The appropriateness of those studies will be determined using the methods described above.

To identify relevant published literature for KQs, we will search the following databases: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, and Cochrane Central Register of Controlled Trials via OVID. We will search clinicaltrials.gov and the World Health Organization International Controlled Trials Registry Platform (ICTRP) for ongoing studies as well as those completed with results, when available. AHRQ will notify the public about the opportunity to submit materials for consideration by the EPC through the Supplemental Evidence and Data for Systematic Review (SEADS) portal through the EHC listserv. The reference list of key articles and systematic reviews or guidelines identified during the article screening process will be reviewed for additional eligible studies.

Articles retrieved through electronic database searching will be screened for inclusion in this review against the established PICOTS framework and inclusion/exclusion criteria. Two independent reviewers will screen each article and agree upon the inclusion/exclusion decision. Disagreements will be resolved through consensus or adjudication in consultation with a third reviewer. With citations retrieved through the search for KQs, the title and abstract of each article will be reviewed by two independent investigators and the article will be excluded if both reviewers agree that it meets one or more exclusion criteria. Articles identified for inclusion will advance to the full-text screening. Articles that meet inclusion/exclusion criteria will be eligible for data abstraction. When necessary, we may contact authors of candidate articles for clarification of reported study details in order to assess for inclusion/exclusion. For articles excluded at the full-text level, we will record the reason for exclusion and present a list of such studies in the review. Citations will be managed using Distiller[®].

Abstracts and meeting presentations will be considered for inclusion into the review if the abstract or presentation can be matched to an original publication that has been included into the review. The original full publication will always be used as the primary data source in the event discrepant data is reported in multiple publications. Post-hoc and

subgroup analyses of included studies will be considered when they provide data on the outcomes of interest.

Data Abstraction and Data Management – Data will be abstracted using Distiller by two trained researchers. The second reviewer will confirm the first reviewer’s abstracted data for completeness and accuracy. A third reviewer will audit a random sample of articles to ensure consistency of the process.

Articles referring to the same study will be abstracted on a single review form, assuming the populations are the same. Authors of individual studies may be contacted either for clarification or to request additional data, if necessary.

For all included studies, reviewers will extract data on study characteristics (e.g. study design, duration of follow-up), eligibility criteria, study population (e.g. age, gender, race/ethnicity, and pain severity), interventions (e.g. intervention drug(s), comparison, dose, frequency, and concomitant medications), outcome measures, and the results of each outcome, including measures of variability.

Assessment of Methodological Risk of Bias of Individual Studies - The assessment of risk of bias for included RCTs of pharmacologic interventions will be performed using the Cochrane Collaboration’s Risk of Bias Tool.¹⁷ For non-randomized studies, we will use the Newcastle Ottawa Scale.¹⁸

Two reviewers will independently assess the risk of bias of each included study, with disagreements resolved by either discussion or consultation with a third team member. The overall risk of bias for each study will be classified as low, moderate or high, according to the collective risk of bias per evaluated domain and the investigator’s confidence in the study results given the identified limitations.¹⁹

Data Synthesis - For each KQ, we will create a set of detailed evidence tables containing all information extracted from included studies. We will synthesize data for traumatic and non-traumatic pain separately. Our primary analgesic comparisons will be opioids (fentanyl or morphine) compared to each non-opioid analgesic (NSAIDs, acetaminophen, ketamine, nitrous oxide, ketamine combined with an either fentanyl or morphine) and these comparisons will be graded for strength of evidence. We will present other comparisons (non-opioids to non-opioids or opioids to opioids) as supplemental analyses within the appendix of the report and these comparisons will not be graded for strength of evidence.

We will perform random-effects meta-analysis using the Hartung-Knapp adjustment when sufficient data for a given outcome is available from at least two studies that are sufficiently homogenous with respect to key clinical (population characteristics, study duration, and intervention) and methodologic (based on risk of bias assessment) variables. Between-study variance will be estimated using the Paule-Mandel estimator.²⁰ Continuous outcomes will be reported as mean differences or standardized mean differences and 95% confidence intervals (CIs). Binary outcomes will be reported as risk ratios (RRs) and absolute risk differences along with 95% CIs. If outcomes are rarely

reported, we will consider use of appropriate methods depending on factors such as overall event rates, the balance of events between arms, and instances of zero events in one study arm or in the study altogether.²¹⁻²⁶ Statistical significance will be set at a two sided alpha of 0.05. All studies, including those that are not amenable to pooling, will be qualitatively summarized.

When quantitative pooling of studies is possible, we will assess for the presence of statistical heterogeneity using the Cochrane p-value ($p < 0.10$ considered significant) and the I^2 statistic which represents the percentage (0-100%) of variation in the treatment estimate that is attributable to heterogeneity, with values $> 50\%$ representing substantial variation.²⁷ We will attempt to determine potential reasons by conducting relevant subgroup analyses based on those subgroups listed in the analytic framework.

To assess for the presence of publication bias, visual inspection of funnel plots will be considered for each pooled analysis. Tests for funnel plot asymmetry (chosen depending on the metric and amount of between-study heterogeneity) will be conducted when 10 or greater studies report the outcome.²⁸⁻³⁰ All analyses were performed using the 'meta' package in R (version 3.5.1; the R Project for Statistical Computing).

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

We will grade the SOE based on the guidance established for the EPC program.³¹ We plan to grade the comparisons of opioids (fentanyl or morphine) to each non-opioid analgesic (NSAIDS, acetaminophen, ketamine, nitrous oxide, ketamine combined with an either fentanyl or morphine) separately for the populations of traumatic pain and non-traumatic pain. The outcomes that were prioritized for grading include pain severity, presence of pain, time to analgesic effect, respiratory depression, hypotension, change in mental status, and total ADEs.

At the completion of the review, two reviewers will independently grade the SOE. Conflicts will be resolved either through consensus or third-party adjudication. Evidence overview tables will include effect estimates and confidence intervals where quantitative synthesis is possible. Overall conclusions and SOE will be assessed considering how the effect estimates and the confidence intervals compare to clinically important differences and consider consistency, precision, and other study limitations. The clinically important differences for this review are summarized in Table 2, reflecting input from our EPC, the sponsor, consultants and the TEP.

Table 2. Clinically important differences for graded outcomes

Outcome	Clinically important difference
Pain score	2 points on a continuous scale
Presence of pain, hypotension, respiratory depression, mental status changes	ARD of 5%
Time to analgesic effect	5 minutes on a continuous scale
Total adverse events	ARD of 10%

Abbreviations: ARD=absolute risk difference

The SOE approach incorporates five key domains: study limitations, directness, consistency, precision, and reporting bias of the evidence body. Additional domains (plausible confounding, dose-response, and magnitude of effect) will be considered when applicable. The SOE pertaining to each KQ will be classified into four categories:

- 1) High – We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- 2) Moderate – We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe the findings are likely to be stable, but some doubt remains.
- 3) Low – We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- 4) Insufficient – We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of the effect for this outcome. No evidence is available of the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Assessing Applicability – We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our KQs as recommended by the EPC methods guide.¹⁶ We will consider how patient age (pediatric vs. adult populations), intervention features (co-interventions and route of administration), and setting (e.g., EMS versus battlefield) may cause heterogeneity of treatment effects and affect generalizability of the findings.

CONTEXTUAL QUESTIONS

To address the first contextual question, we will consult the package inserts of specific analgesics and consideration of exclusion criteria from studies included in KQs 1-4 in order to narratively summarize the relevant contraindications. To address the second contextual question, we will conduct a literature scan in the prehospital, emergency department and battlefield settings to present a narrative summary of how the specific pain

assessment tools perform (accuracy, correlations, and interrater reliability) within the pre-specified special populations.

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VI. Definition of Terms

Not applicable

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
1/28/19	II. Key Questions	Outcomes for KQ2 and 4 included: heart rate, respiratory rate, respiratory depression, hypotension, nausea, vomiting, mental status changes, emergence delirium, any adverse event (as in any subject that experienced an adverse event during the study period).	Adding the following outcomes to KQ 2 and 4: systolic blood pressure, diastolic blood pressure, oxygen saturation	Respiratory depression and hypotension were prioritized as important outcomes. In the absence of robust data for these harms, decisionmakers may be interested in changes in blood pressure and oxygen saturation.

VIII. Review of Key Questions

The Evidence-based Practice Center (EPC) refined and finalized the key questions with input from the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. 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.

X. 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.

XI. 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.

XII. Role of the Funder

This project was funded under Contract No. HHSA290201500012I 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.

XIII. Registration

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

Appendix A

Search in MEDLINE

1. Emergency Medical Services/
2. Emergency Medical Technicians/
3. Emergency Treatment/
4. Emergency Medicine/
5. AMBULANCES/ or AIR AMBULANCES/
6. First Aid/
7. prehospital.mp.
8. pre-hospital.mp.
9. paramedic*.mp.
10. ambulance*.mp.
11. out-of-hospital.mp.
12. out of hospital.mp.
13. ems.mp.
14. emt.mp.
15. emergency services.mp.
16. emergency medical service*.mp.
17. emergency technician*.mp.
18. emergency practitioner.mp.
19. emergency dispatch*.mp.
20. emergency despatch*.mp.
21. first responder*.mp.
22. emergency rescue*.mp.
23. emergency resus*.mp.
24. emergency triage.mp.
25. military medicine/
26. military medicine.mp
27. battlefield.mp
28. combat.mp
29. emergency department.mp
30. hospital/
31. morphine/
32. fentanyl/
33. ketamine/
34. nitrous oxide/
35. ketorolac/
36. ketorolac tromethamine/
37. ibuprofen/
38. acetaminophen/
39. morphine.mp
40. ketamine.mp
41. ketorolac.mp
42. fentanyl.mp
43. nitrous oxide*.mp
44. ibuprofen.mp

45. acetaminophen.mp
46. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
48. 46 and 47
49. epidemiologic studies/
50. exp cohort studies/
51. exp case-control studies/
52. case control.tw.
53. (cohort adj (study or studies)).tw.
54. cohort analy\$.tw.
55. (follow up adj (study or studies)).tw.
56. (observational adj (study or studies)).tw.
57. longitudinal.tw.
58. retrospective.tw.
59. cross sectional.tw.
60. cross-sectional studies/
61. or/49-60
62. randomized controlled trials as topic/
63. randomized controlled trial/
64. random allocation/
65. double blind method/
66. single blind method/
67. clinical trial/
68. clinical trial, phase i.pt.
69. clinical trial, phase ii.pt.
70. clinical trial, phase iii.pt.
71. clinical trial, phase iv.pt.
72. controlled clinical trial.pt.
73. randomized controlled trial.pt.
74. multicenter study.pt.
75. clinical trial.pt.
76. exp clinical trials as topic/
77. or/62-76
78. (clinical adj trial\$).tw.
79. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
80. placebos/
81. placebo\$.tw.
82. randomly allocated.tw.
83. (allocated adj2 random\$).tw.
84. or/78-83
85. 77 or 84
86. case report.tw.
87. letter/
88. historical article/
89. or/86-88

90. 85 not 89
91. 61 or 90
92. 91 and 48