



## Evidence-based Practice Center Systematic Review Protocol

Project Title: Management of suspected opioid overdose with *Naloxone* by *Emergency Medical Services personnel*

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

Abuse and overdoses associated with prescription and illicit opioids have been characterized by the U.S. Department of Health and Human Services as a national crisis.<sup>1</sup> Since 2000, the rate of overdose deaths involving opioids has increased four-fold.<sup>2,3</sup> Drug overdose deaths are now the leading cause of injury death in the United States.<sup>4</sup> Overdoses due to opioids occur as a result of their central nervous system effects, which cause respiratory depression that can progress to cardiac arrest if untreated. In 2014, the number of drug overdose deaths involving prescription or illicit opioids exceeded 28,000, the highest number on record.<sup>3</sup> The strongest risk factor for opioid overdose is a prior overdose event. Other risk factors include concomitant use of other medications and substances with central nervous system depressant effects, recent abstinence (due to decreased tolerance to opioids upon re-exposure), use of illicit opioids, higher doses of opioids, obtaining opioids from multiple providers or pharmacies, presence of comorbid conditions such as sleep apnea or other respiratory disease, and genetic predisposition to the respiratory depressant effects of opioids.<sup>5-10</sup> Children in households with an adult who is prescribed opioids are also at risk for overdose.<sup>11,12</sup> The increase in overdoses may be in part a consequence of increased opioid prescribing; about 80%<sup>13,14</sup> of heroin users now report that they were first exposed to opioids through a prescription.<sup>15</sup> Opioid overdoses have serious adverse health consequences, even when not fatal; although difficult to estimate, the ratio of fatal to nonfatal overdoses may range from 7.5:1 to 30:1.<sup>16,17</sup>

Naloxone is an opioid antagonist used to rapidly counteract the central nervous system (CNS) and respiratory depressant effects of opioids, potentially preventing fatal overdose.<sup>18</sup> Naloxone can be administered by the intravenous (IV), intramuscular (IM), subcutaneous (SC), intranasal (IN), endotracheal (ET), nebulized/inhalational, buccal or sublingual routes.<sup>19</sup> The U.S. Food and Drug Administration approved a handheld naloxone IM or SC auto-injector in 2014<sup>20</sup> and a new intranasal formulation in 2015;<sup>21</sup> both administer a preset dose and are easy to use. With administration using a preloaded IN system, there is no risk of needle stick injury. Beyond clinical settings, naloxone also appears to decrease the risk of opioid overdose when distributed in community-based programs.<sup>22-24</sup> Naloxone may precipitate withdrawal symptoms,<sup>25</sup> which while uncomfortable, are generally not serious or life-threatening and generally short-lived; the half-life of naloxone is about 30 minutes. Post withdrawal agitation following naloxone administration may also put the person giving the naloxone at increased risk.<sup>26,27</sup> Withdrawal symptoms may be more severe with use of IV naloxone and may be minimized by using the lowest effective doses and dose titration.<sup>18,25</sup>

Emergency medical services (EMS) personnel play a vital role in the management of potential opioid overdoses. Early intervention by EMS personnel is critical to prevent death and other complications of opioid overdose.<sup>28</sup> Airway management and continuous

assessment of oxygenation and ventilation, along with administration of naloxone, is the standard of care for EMS personnel treating opioid overdoses.<sup>29</sup> The number of EMS encounters for suspected opioid overdose has increased,<sup>30</sup> with nearly 160,000 doses of naloxone administered by EMS personnel in 2014.<sup>30</sup> Regulations vary, however, with regard to what EMS personnel with different levels of training are permitted with regard to administration of naloxone. In order of increasing level of training, EMS personnel are commonly classified as emergency medical responders (EMRs), emergency medical technicians (EMTs), intermediate/advanced EMTs, and paramedics (in most states, the intermediate EMT classification has been replaced by advanced EMTs).<sup>31</sup> Naloxone administration is not currently within the National EMS Scope of Practice Model for EMTs and EMRs, which was last updated in 2007,<sup>31</sup> prior to the introduction of newer naloxone formulations and availability of newer evidence on the benefits of field use of naloxone. A recent systematic review<sup>32</sup> of U.S. laws, regulations, and policies found that all jurisdictions permitted paramedics and 48 permitted intermediate life support personnel to administer naloxone. Fewer jurisdictions permitted basic life support personnel to administer naloxone, which may contribute to disparities in areas in which more care is provided by EMRs and EMTs.<sup>33</sup>

Although a number of recommendations, guidelines, and protocols are available to inform out-of-hospital management of opioid overdose patients, including naloxone use, guidance varies across these documents, and there are uncertainties in a number of areas.<sup>34-36</sup> These include the optimal route of administration, the optimal dose for different routes of administration, optimal dosing strategies, and training levels for EMS personnel who are permitted to administer naloxone. The 2015 American Heart Association guideline update for cardiopulmonary resuscitation and emergency cardiovascular care notes that the ideal dose of naloxone is not known; an empiric starting dose of 0.04 to 0.4 mg IV or IM is recommended to avoid provoking severe opioid withdrawal and to allow for a range of doses depending on the clinical scenario, with repeat doses or dose escalation to 2 mg if the initial response is inadequate.<sup>34</sup> The naloxone auto-injectors originally approved by the FDA administered a dose of 0.4 mg; a 2 mg dose was approved in 2016. For IN naloxone, the guideline also notes that most studies used a fixed dose of 2 mg, repeated in 3 to 5 minutes if necessary; however, the nasal spray approved by the FDA in 2015 administers a dose of 4 mg in a more concentrated solution of 0.1 mL. Concentrated solutions may be necessary for optimal IN administration due to a low rate of absorption (a high proportion of IN naloxone is swallowed and inert) and because a maximum of 0.5 mL can be delivered per nostril. The effectiveness of current dosing guidelines for reversing overdose due to highly potent synthetic opioids such as carfentanil, which has become increasingly available on the streets, is also uncertain.<sup>37</sup> There is also uncertainty regarding whether patients should be dosed until they achieve sufficient spontaneous respiration or dosed until they return to full consciousness, and whether hospital transport is medically necessary following successful naloxone treatment of opioid overdose.<sup>38</sup>

The purpose of this systematic review is to synthesize the evidence on naloxone route of administration and dosing for suspected opioid overdose in out-of-hospital settings, and on the need for transport to a hospital following successful opioid overdose reversal with naloxone; the review will inform development of evidence-based guidelines on EMS management of suspected opioid overdose and potentially inform an update to the

National EMS Scope of Practice Model regarding naloxone use across EMS training levels.

## II. The Key Questions

The scope and key questions for this topic were developed by AHRQ in conjunction with federal partners.

Key Question 1: For patients with confirmed or suspected opioid overdose, what is the comparative benefit and harms of out-of-hospital administration of naloxone by EMS personnel using intravenous, intramuscular, subcutaneous, and intranasal routes of administration?

1a. For patients with confirmed or suspected opioid overdose who receive naloxone in the out-of-hospital setting from EMS personnel, what are the comparative benefits and harms of different intravenous, intramuscular, subcutaneous, or intranasal, or intramuscular doses of naloxone?

Key Question 2: For patients with confirmed or suspected opioid overdose in out-of-hospital settings, what is the comparative benefit and harms of titration of naloxone administered by EMS personnel until the patient resumes sufficient spontaneous respiratory effort versus until the patient regains consciousness?

Key Question 3: For patients with confirmed or suspected opioid overdose in out-of-hospital settings treated with multiple doses of naloxone (including patients who do not improve after an initial dose of intranasal naloxone), what are the effects on benefits and harms of differences in timing of repeat dosing?

Key Question 4: For patients with confirmed or suspected opioid overdose in out-of-hospital settings who regain sufficient spontaneous respiratory effort and are alert and oriented after naloxone administration by EMS personnel, what are the benefits and harms of transporting patients to a healthcare facility versus non-transport?

- Population(s):
  - *Include:* Persons with confirmed or suspected opioid overdose who exhibit altered mental status, miosis or respiratory depression and who are treated in the out-of-hospital setting by EMS personnel
    - Will also include studies of naloxone administration in out-of-hospital settings by non-EMS personnel (e.g., police, other first responders, laypersons), which may inform optimal dosing strategies in EMS personnel
  - Subpopulations: Based on age, sex, race, type of opioid involved in overdose, dose of opioid involved in overdose, presence of other drugs or substances contributing to overdose, estimated time since overdose, concomitant psychiatric comorbidities, prior overdose episodes
  - *Exclude:* Patients with altered mental status or respiratory distress due solely to trauma, hypoxia or ethanol ingestion, and patients without signs of opioid overdose treated for chronic pain or addiction with buprenorphine/naloxone.

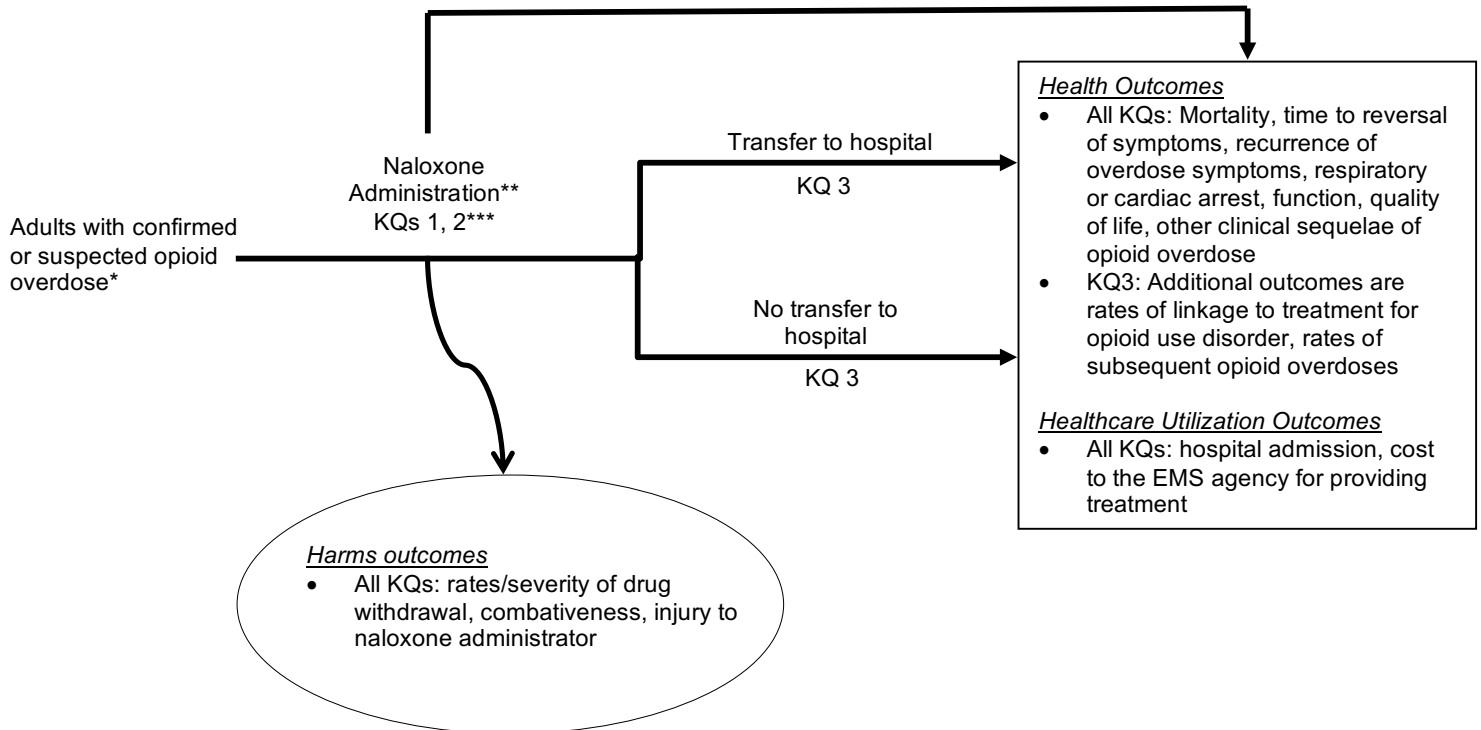
- Interventions:

Included Drug	Dose and Route of Administration
Naloxone	<ul style="list-style-type: none"> <li>• Auto-injector, intramuscular (IM) 0.4mg/0.4mL, 2 mg/0.4 mL</li> <li>• Nasal spray, intranasal (IN) 4 mg/0.1 mL, 2 mg/2 mL</li> <li>• Injection, intravenous, intramuscular or subcutaneous 0.4 mg/mL, 0.2 mg/mL, 1 mg/mL, 2 mg/mL</li> </ul>

- Potential modifiers of interventions: Based on training and background of the person administering naloxone
- *Exclude:* Naloxone in combination with other medications (e.g., Suboxone)
- For Key Question 4: *Include* Transport to healthcare facility
- Comparators:
  - *Key Question 1:* Injection (intramuscular, subcutaneous or intravenous) versus intranasal route of administration
  - *Key Question 1a:* Comparisons of different doses of intranasal, intramuscular, and intravenous naloxone
  - *Key Question 2:* Titration of patients until they resume spontaneous respiration but have some residual sedation/altered mental status versus dosing of patient until they resume spontaneous respiration and are awake and alert
  - *Key Question 3:* Comparison of differences in timing of repeat dosing
  - *Key Question 4:* Transport of patients following treatment of opioid overdose with naloxone to a healthcare facility vs. non-transport
- Outcomes for each question:
  - *All key questions:* Mortality, time to reversal of symptoms, recurrence of overdose symptoms, respiratory or cardiac arrest, function, quality of life, other clinical sequelae of opioid overdose; healthcare utilization indicators (e.g., hospital admission, cost to the EMS agency for providing treatment); and adverse effects and other harms (such as rates/severity of drug withdrawal, combativeness, injury to naloxone administrator)
  - *Key Question 4:* Additional outcomes are rates of linkage to treatment for opioid use disorder, rates of subsequent opioid overdoses
- Timing:
  - Naloxone administered in the out-of-hospital setting
- Settings:
  - *Include:* Out-of-hospital setting, Emergency Department (ED) setting (for Key Question 1a)
  - *Exclude:* Inpatient, Clinic, or Emergency Department (ED) setting (for Key Questions other than 1a)
- **Study Designs**
  - Randomized trials

- Cohort and case-control studies
- For comparisons related to different doses, a preliminary search indicated that there are few head-to-head studies directly comparing different doses. If this is confirmed, we will include placebo-controlled studies that evaluated single doses for the purpose of potentially informing indirect comparisons related to dosing.

### III. Analytic Framework



\* Persons with confirmed or suspected opioid overdose who exhibit altered mental status, miosis or respiratory distress and who are treated in the out-of-hospital setting by Emergency Medical Services personnel.

\*\*Administration of naloxone hydrochloride via the nasal, intravenous, intramuscular or subcutaneous injection (including the naloxone auto-injector).

\*\*\*KQ1 addresses comparisons involving route of administration and dose; KQ 2 addresses comparisons involving dose titration to varying degrees of return of consciousness (intermediate outcome).

## IV. Methods

### Criteria for Inclusion/Exclusion of Studies in the Review –

The criteria for inclusion and exclusion of studies will be based on the Key Questions and are described in the PICOTS section above.

Below are additional details on the scope of this project:

Study Designs: We will include randomized trials. Due to the expected small numbers of randomized controlled trials to address the Key Questions, we also plan to include cohort and case-control studies.

Non-English Language Studies: We will restrict to English-language articles, but will review English language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria, in order to assess for the likelihood of language bias.

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

Publication Date Range: We will include studies with any publication date.

Literature Databases: Ovid MEDLINE, PsycINFO, the Cochrane Central Register of Controlled Trials (CCRCT), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) will be searched to capture published literature. Preliminary search strategies are available in **Appendix A**.

Scientific Information Packets: The AHRQ Evidence-based Practice Center (EPC) Scientific Resource Center (SRC) will send email notification to relevant stakeholders about the opportunity to submit Scientific Information Packets (SIP) via the Effective Health Care (EHC) Web site for the pharmaceutical interventions listed in the Key Questions. These contain both published and unpublished evidence relevant to the review and will be reviewed according to the criteria and processes described for all evidence, below.

Hand Searching: Reference lists of included articles will be reviewed for includable literature.

Grey literature: Sources for grey (unpublished) literature will include any SIPs that are received and searches on the ClinicalTrials.gov trial registry to identify trials that are in-progress or have been completed.

Contacting Authors: In the event that information regarding methods or results appears to be omitted from the published results of a study, or if we are aware of unpublished data, we will query the authors to obtain additional information.

Process for Selecting Studies: Pre-established criteria will be used to determine eligibility for inclusion and exclusion of abstracts in accordance with the AHRQ EPC Methods Guide.<sup>39</sup> To ensure accuracy, all excluded abstracts will be independently reviewed by at least two investigators. All citations deemed appropriate for inclusion by at least one of the reviewers will be retrieved. Each full-text article will be independently reviewed for eligibility by at least two investigators, including any articles suggested by peer reviewers or that arise from the public posting or SIP processes. Any disagreements will be resolved by consensus.

#### Data Abstraction and Data Management

After studies are deemed to meet inclusion criteria, the following data will be abstracted: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics (age, sex, race, type of opioid involved in overdose, dose of opioid involved in overdose, presence of other drugs or substances contributing to overdose, estimated time since overdose, concomitant psychiatric comorbidities, prior overdose episodes), intervention characteristics (route of administration dosage, duration, training/background of personnel administering drug), and results relevant to each key question as outlined in the previous PICOTS section. Information that will be abstracted that is relevant for assessing applicability will include the number of patients randomized/eligible for inclusion in an observational study relative to the number of patients enrolled, and characteristics of the population, intervention, administering personnel. Sources of funding for all studies will also be recorded. All study data will be verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

#### Assessment of Methodological Risk of Bias of Individual Studies

Predefined criteria will be used to assess the risk of bias for individual controlled trials, and observational studies by using clearly defined templates and criteria as appropriate. Studies will be evaluated using appropriate study-design specific criteria developed by the U.S. Preventive Services Task Force.<sup>40</sup> These criteria and methods will be used in conjunction with the approach recommended in the chapter, *Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions in the AHRQ EPC Methods Guide*.<sup>41</sup> Studies will be rated as “low risk of bias,” “medium risk of bias,” or “high risk of bias.”

Studies rated “low risk of bias” are considered to have the least risk of bias, and their results are generally considered valid. “Low risk of bias” studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated “medium risk of bias” are susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of low



risk of bias, but no flaw likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The “medium risk of bias” category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some medium risk of bias studies are likely to be valid, while others may be only possibly valid.

Studies rated “high risk of bias” have significant flaws that imply biases of various types that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. In general observational studies that do not perform adjustment for potential confounders will be assessed as “high risk of bias.” The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared interventions. We will not exclude studies rated high risk of bias a priori, but high risk of bias studies will be considered to be less reliable than low or medium risk of bias studies when synthesizing the evidence, particularly if discrepancies between studies are present.

Each study evaluated will be independently reviewed for risk of bias by two team members. Any disagreements will be resolved by consensus. Team members who were involved in the conduct of a study will not be involved in data abstraction or risk of bias assessment for that study.

#### Data Synthesis

We will construct evidence tables identifying the study characteristics (as discussed above), results of interest, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. We will review and highlight studies by using a hierarchy-of-evidence approach, where the best evidence is the focus of our synthesis for each key question.

Qualitative data will be summarized in summary tables and as ranges and descriptive analysis and interpretation of the results will be provided.

If sufficient data are available, meta-analyses will be conducted to summarize data and obtain more precise estimates on outcomes for which studies are homogeneous enough to provide a meaningful combined estimate. The feasibility of a quantitative synthesis will depend on the number and completeness of reported outcomes and a lack of heterogeneity among the reported results. To determine whether meta-analysis could be meaningfully performed, we will consider the risk of bias for each of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes, and may conduct sensitivity analyses. If meta-analysis is performed, randomized controlled trials will be analyzed separately from observational studies. Meta-regression may be conducted to explore statistical heterogeneity using additional variables on methodological or other characteristics (e.g., risk of bias, randomization or blinding, outcome definition and ascertainment) given enough number of studies.



For comparisons involving effects of different doses of intranasal, intramuscular, subcutaneous, or intravenous naloxone, a preliminary search indicated few head-to-head studies. If this is confirmed, we will attempt to assess effects of dose using indirect comparisons, based on cross-study comparisons of studies that utilize different doses.

Results will be presented as structured by the key questions, and any prioritized outcomes will be presented first. Prioritization of outcomes will be determined with input from the Technical Expert Panel (TEP).

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

The strength of evidence for each key question will be initially assessed by one researcher for prioritized clinical outcomes (mortality, time to reversal of symptoms, recurrence of overdose symptoms, respiratory or cardiac arrest, rates/severity of drug withdrawal; and combativeness) by using the approach described in the AHRQ EPC Methods Guide.<sup>41</sup> To ensure consistency and validity of the evaluation, the grades will be reviewed by the entire team of investigators, and based on assessments of the following domains:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting bias (suspected or undetected)

The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

- 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.
- 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 that the findings are likely to be stable, but some doubt remains.
- 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.
- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion

Assessing Applicability—Applicability will be considered according to the approach described in the AHRQ Methods Guide.<sup>42</sup> We will use the PICOTs framework to consider the applicability of the evidence base for each key question, for example examining the characteristics of the patient populations (e.g., age [including the proportion of patients >65 years of age], duration of overdose, and opioids involved in the overdose, if known [in particular, involvement of long-acting opioids or high-potency synthetic opioids]); and study setting (e.g., field versus clinical setting). Variability in the studies may limit the ability to generalize the results to other populations and settings.

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## VI. Definition of Terms

Not applicable.

## 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.

## VIII. Review of Key Questions

Not applicable to this project.

## IX. Key Informants

Not applicable to this project.

## 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 health 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, recommend approaches to specific methodological issues as requested by the EPC, and provide input on clinical and technical issues. 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 \$10,000 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 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 \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. 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.

HHSA290201500009I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The 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).

## Appendix A. Search strategies

### MEDLINE:

Database: Ovid MEDLINE(R) <1946 to August Week 2 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 18, 2016>

- 1 overdose\*.mp.
- 2 drug overdose/ or opioid-related disorders/
- 3 Naloxone/ or naloxone.mp.
- 4 (1 or 2) and 3

### PsycINFO

Database: PsycINFO <1806 to July Week 4 2016>

- 1 naloxone.mp. or exp NALOXONE/
- 2 exp DRUG OVERDOSES/
- 3 overdos\*.mp.
- 4 1 and (2 or 3)

### CCRCT:

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2016>

- 1 naloxone.mp. or exp NALOXONE/
- 2 exp DRUG OVERDOSES/
- 3 overdos\*.mp.
- 4 1 and (2 or 3)

### CINAHL:

((MH "Naloxone") OR "naloxone") AND ((MH "Overdose") OR "overdose" OR overdos\*)