

## Evidence-based Practice Center Systematic Review Protocol

Project Title: The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain

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

Chronic pain, often defined as pain lasting longer than 3 months or past the time of normal tissue healing, is extremely common. According to a recent Institute of Medicine report, up to one-third of U.S. adults report chronic pain.<sup>1</sup> Chronic pain is by definition persistent, and frequently difficult to treat. There has been a dramatic increase over the past 10 to 20 years in the prescription of opioid medications for chronic pain, despite limited evidence showing long-term beneficial effects. In addition, accumulating evidence indicates increasing rates of harms associated with prescription opioids, including accidental overdose, abuse, addiction, diversion, and accidents involving injuries (such as falls and motor vehicle accidents).<sup>2-12</sup> Of perhaps most concern is the dramatic increase in overdose deaths associated with opioids. In 2010, there were 16,651 fatal overdoses involving prescription opioids.<sup>13</sup> Prescription opioid misuse and abuse resulted in over 400,000 emergency department visits in 2010, over twice as many as in 2004.<sup>5</sup> Substance abuse treatment admissions for opiates other than heroin increased more than six-fold from 1999 to 2009.<sup>4</sup> Opioids are also associated with other well-known adverse effects such as constipation, nausea, and sedation.<sup>14</sup> More recent data have reported potential associations between use of long-term opioid therapy and other harms such as adverse endocrinological effects and hyperalgesia.<sup>15-17</sup>

These data underscore the complexity of clinical decision-making around long-term opioid therapy, which requires individualized assessments of the balance between benefits and harms, decisions related to opioid selection and dose initiation and titration strategies, integration of risk assessment and mitigation strategies, and consideration of the role of alternative, non-opioid therapies. For example, recent data have shown an association between opioid use and overdose death that is dose-dependent,<sup>8, 18, 19</sup> suggesting that application of maximum dose ceilings could be one strategy to reduce overdose risk. Risk mitigation strategies that have been suggested in patients prescribed opioids include use of opioid medication agreements, regular clinical followup and monitoring, urine drug screens, and use of data from prescription drug monitoring programs.<sup>20</sup>

Challenges in conducting a systematic literature review on long-term opioid therapy include the breadth of topics that must be addressed; the potential variability in benefits and harms depending on patient characteristics, opioid characteristics (e.g., short- vs. long-acting and dose), dosing strategies, and characteristics of the clinical setting; limitations in generalizability due to study design and other methodological shortcomings (e.g., duration of followup, exclusion of patients at higher risk for harms, or underrepresentation of certain sociodemographic groups); and gaps in research on important scientific questions.<sup>21</sup> Although guidelines on use of opioids for chronic pain are available, most recommendations were based on weak or limited evidence.<sup>20, 22</sup> The

observed increase in harms associated with long-term opioid therapy, continued wide variations in practice related to long-term opioid therapy, and the availability of new evidence underscore the need for a current systematic review in this area.

This topic was nominated by the National Institutes of Health, which has convened a Working Group to assist in refining the topic. Although guidelines from the American Pain Society/American Academy of Pain Medicine,<sup>20</sup> the Veterans Administration/Department of Defense,<sup>23</sup> and other groups have been published, the availability of new evidence warrants a new systematic review that could be used to inform updated or new guidelines, guide quality improvement efforts, and define and update priorities for further research in this area.<sup>21</sup> To aid in the efficiency of the review process, this review will be conducted as an update of a prior systematic review on long-term opioid therapy funded by the American Pain Society and conducted by the same review team.<sup>24</sup>

## **II. The Key Questions**

### **I. Effectiveness and comparative effectiveness**

- a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (>1 year) outcomes related to pain, function, and quality of life?
- b. How does effectiveness vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); 2) patient demographics (e.g., age, race, ethnicity, gender); 3) patient comorbidities (including past or current alcohol or substance abuse and related disorders, mental health disorder and those at high risk for addiction and medical comorbidities)?
- c. In patients with chronic pain, what is the comparative effectiveness of opioids versus non-opioid therapies (pharmacological or non-pharmacological) on outcomes related to pain, function, and quality of life?
- d. In patients with chronic pain, what is the comparative effectiveness of opioids plus non-opioid interventions (pharmacological or non-pharmacological) versus opioids or non-opioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

### **II. Harms and adverse events**

- a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: 1) opioid abuse, addiction, and related outcomes; 2) overdose; and 3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?
- b. How do harms vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); 2) patient demographics; 3) patient

comorbidities (including past or current addictive disorder or at high risk for addiction); 4) the dose of opioids used?

### III. Dosing strategies

- a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risks of overdose, addiction, abuse, or misuse; and doses of opioids used?
- b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?
- d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids vs. long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of maximum dose ceilings on outcomes related to pain, function, and quality of life?
- g. In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?
- h. In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?
- i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?
- j. In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?

### IV. Risk assessment and risk mitigation strategies

- a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?
- b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?
- c. In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including 1) opioid management plans, 2) patient education, 3) urine drug screening, 4) use of prescription drug monitoring program data, 5) use of monitoring instruments, 6) more frequent monitoring intervals, 7) pill counts, and 8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?
- d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?

## PICOTS

- **Population(s):**

- Include:

- For all KQs: Adults (age >18 years) with various types of chronic pain (defined as pain lasting >3 months), including patients with acute exacerbations of chronic pain (KQ Ig)
    - For KQs Ib, IIb: Subgroups as defined by specific pain condition, patient demographics (e.g., age, race, ethnicity, sex), comorbidities (including medical comorbidities and mental health disorders, including past or current alcohol or substance abuse and related disorders, and those at high risk for addiction); For KQ IIb: Subgroups also defined by the dose of opioids used

- Exclude:

- Patients with pain at end of life, acute pain, pregnant or breastfeeding, patients treated with opioids for addiction

- **Interventions:**

- Include:

- For KQs I, II, III: Long- or short-acting opioids (including tapentadol) used as long-term therapy (defined as use of opioids on most days for >3months)
    - For KQ Id: Also include combination of opioid plus non-opioid therapy (pharmacological or non-pharmacological)
    - For KQ IVa, b: Risk prediction instruments
    - For KQ IVc: Opioid management plans, patient education, urine drug

screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, use of abuse e formulations

- For KQ IVd: Opioid management strategies

Exclude:

- Intravenous or intramuscular administration of opioids
- Tramadol

- **Comparators:**

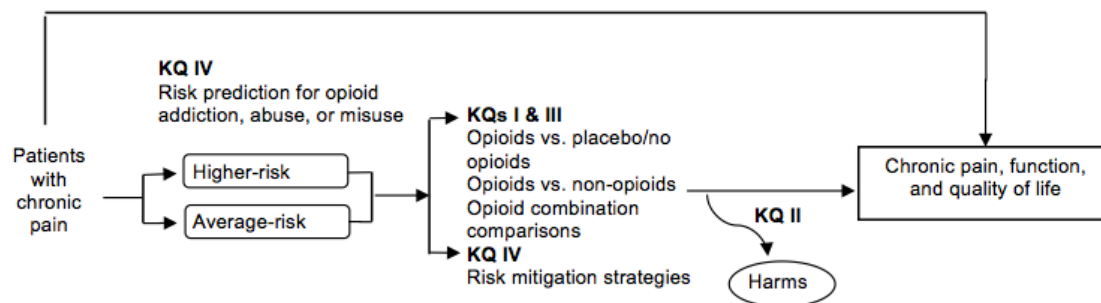
Include:

- For KQs Ia, Ib, IIa, IIb: Opioid vs. placebo or non-opioid therapy (including usual care)
- For KQ Ic: Opioid vs. non-opioid therapy (pharmacological or non-pharmacological [e.g., exercise therapy, cognitive behavioral therapy, interdisciplinary rehabilitation])
- For KQ Id: Opioid plus non-opioid therapy (pharmacological or non-pharmacological) vs. opioid or non-opioid therapy alone
- For KQ IIIa: Comparisons of different dose initiation and titration strategies
- For KQ IIIb: Short- vs. long-acting opioids
- For KQ IIIc: One long-acting opioid vs. another long-acting opioid
- For KQ IIId: Short- plus long-acting opioid vs. long-acting opioid
- For KQ IIIe: Scheduled, continuous vs. as-needed dosing of opioid
- For KQ IIIf: Dose escalation vs. dose maintenance or use of maximum dosing thresholds
- For KQ IIIg: Opioid rotation vs. continuation of current opioid
- For KQ IIIh: Comparisons of different methods for treating acute exacerbations of chronic pain
- For KQ IIIi: Decreasing or tapering opioid doses vs. continuation of opioids
- For KQ IIIj: Comparisons of different tapering protocols and strategies
- For KQ IVa: Risk prediction instruments vs. reference standard for overdose or opioid addiction, abuse or misuse
- For KQ IVb: Risk prediction instruments vs. non-use of risk prediction instruments
- For KQ IVc: Risk mitigation strategies (see Interventions above) vs. non-use of risk mitigation strategies

- For KQ IVd: Comparisons of treatment strategies for managing patients with addiction to prescription opioids
- **Outcomes:**
  - Include:
    - For KQs I, III, IV: Pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression), doses of opioids used
    - Also for KQs II, III, IV: Overdose, opioid use disorder, addiction, abuse, and misuse; other opioid-related harms (including gastrointestinal, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression))
  - Exclude:
    - Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)
- **Timing:**
  - Include:
    - For outcomes related to trauma, injury, or overdose: any duration
    - For other outcomes: >1 year
- **Settings:**
  - Include:
    - Outpatient settings (e.g., primary care, pain clinics, other specialty clinics)
  - Exclude:
    - Addiction treatment settings, inpatient settings

### III. Analytic Framework

**Figure 1. Analytic Framework for the Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain**



### IV. Methods

#### A. 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 previous PICOTS section.

Below are additional details on the scope of this project:

Study Designs: For Key Question IVa, we will include studies that evaluate the predictive ability of risk prediction instruments. We will include randomized controlled trials (RCTs), cohort studies, and case-control studies for all key questions. For all key questions, we will exclude uncontrolled observational studies, case series, and case reports. For Key Question IVa, we will exclude studies that do not evaluate the performance of a risk prediction instrument against a reference standard. Systematic reviews will be used as primary sources of evidence if they address a key question and are assessed as being at low risk of bias, according to the AMSTAR quality assessment tool.<sup>25, 26</sup> If systematic reviews are included, we will update findings with any new primary studies identified in our searches. If multiple systematic reviews are relevant and low risk of bias, we will focus on the findings from the most recent reviews and evaluate areas of consistency and inconsistency across the reviews.<sup>27</sup>

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.

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

Publication Date Range: Searches will begin in January 2008, as a systematic evidence review published by the American Pain Society in conjunction with the American Academy of Pain Medicine<sup>24</sup> addresses many of the key questions in the current review, with searches conducted through October 2008. For Key Questions not covered by the American Pain Society review (Key Questions IIIi and IVd), no search dates will be imposed.

Library searches will be updated while the draft report is posted for public comment and peer review to capture any new publications. Literature identified during the updated search will be assessed by following the same process of dual review as all other studies considered for inclusion in the report. If any pertinent new literature is identified for inclusion in the report, it will be incorporated before the final submission of the report.

Literature Databases: Ovid MEDLINE, PsychINFO, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the National Guideline Clearinghouse will be searched to capture both published and grey literature.

Scientific Information Packets: The current application holders from the U.S. Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) Extended-Release and Long-Acting (ER/LA) Opioid AnalgesicsList<sup>28</sup> will be invited to provide Scientific Information Packets (SIPs).

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

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 this 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 Methods Guide.<sup>25</sup> To ensure accuracy, all excluded abstracts will be dual reviewed. 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 two team members, including any articles suggested by peer reviewers or that arise from the public posting process. Any disagreements will be resolved by consensus. We will review studies included in the prior American Pain Society review to verify that they meet inclusion criteria for the current review.



### **C. Data Abstraction and Data Management**

After studies are selected for inclusion, data will be abstracted into categories that include but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, 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 relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention, and care settings. 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.

### **D. Assessment of Methodological Risk of Bias of Individual Studies**

Predefined criteria will be used to assess the quality of individual controlled trials, systematic reviews, and observational studies by using clearly defined templates and criteria as appropriate. Randomized trials will be evaluated with appropriate criteria and methods developed by the Cochrane Back Review Group<sup>29</sup> and cohort and other observational studies will be evaluated using appropriate criteria developed by the U.S. Preventive Services Task Force.<sup>30</sup> Systematic reviews will be assessed using the AMSTAR quality rating instrument.<sup>26</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<sup>25</sup> in the AHRQ Methods Guide developed by the Agency for Healthcare Research and Quality. Studies will be rated as “good,” “fair,” or “poor,” or as specified by the particular criteria. We will re-review the quality ratings of studies included in the prior American Pain Society review to insure consistency in quality assessment.

Studies rated “good” will be considered to have the least risk of bias, and their results will be considered valid. Good-quality 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 “fair” will be susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated “poor” will have significant flaws that imply biases of various types that may invalidate the results. They will 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. The results of these studies will be least as likely to reflect flaws in the study design as the true difference between the compared interventions. We will not exclude studies rated as being poor in quality a priori, but poor-quality studies will be considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present.

Each study evaluated will be dual-reviewed for quality by two team members. Any disagreements will be resolved by consensus.

## **E. Data Synthesis**

We will construct evidence tables identifying the study characteristics (as discussed above), results of interest, and quality 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. In the evidence tables, we will include relevant studies from the prior American Pain Society review as well as new studies identified in current searches.

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

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 quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes, and may conduct sensitivity analyses. The key questions are designed to assess the comparative effectiveness and harms by patient demographics, comorbidities, pain types, treatment features and dosing strategies. Meta-regression may be conducted to explore statistical heterogeneity using additional variables on methodological or other characteristics (e.g., quality, randomization or blinding, outcome definition and ascertainment) given enough number of studies.

Results will be presented as structured by the key questions, and any prioritized outcomes will be presented first.

## **F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes**

The strength of evidence for each key question will be initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.<sup>25 25</sup> To ensure consistency and validity of the evaluation, the grades will be reviewed by the entire team of investigators for:

- 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.

## **G. Assessing Applicability**

Applicability will be estimated by examining the characteristics of the patient populations (e.g., demographic characteristics, duration or severity of pain, underlying pain condition, presence of medical and psychiatric co-morbidities); the sample size of the studies; and clinical settings (e.g., primary care, specialty setting) and countries (e.g., patients in developing countries) in which the studies are performed. Variability in the studies may limit the ability to generalize the results to other populations and settings.

## V. References

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## VI. Definition of Terms

Not applicable.

## VII. Summary of Protocol Amendments

Not applicable.

## VIII. Review of Key Questions

Key questions were reviewed and refined as needed by the EPC with input from the NIH Working Group and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

## IX. NIH Working Group

In place of Key Informants, a NIH Working Group Planning Meeting occurred to provide input into identifying the key questions and guiding the scope of the report, because this topic was nominated to AHRQ from the National Institutes of Health.

## **X. Technical Experts**

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and 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 methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential 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, which cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

### **XIII. Role of the Funder**

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## APPENDIX

### Sample Search Strategy (Ovid MEDLINE)

PICOTS	Search terms
Population: Chronic pain	1. exp Chronic Pain/ 2. (chronic adj2 pain).mp 3. or/1-2
Population: Patients with or at risk of opioid addiction	4. Opioid-Related Disorders/ 5. (opioid adj2 (abuse or addict* or misuse or diversion)).mp 6. or/4-5
Intervention: Opioids (includes alone and in combination with other pharmacologic and non- pharmacologic interventions)	7. exp Analgesics, Opioid/ 8. opioid*.mp 9. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or dextorphan or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp 10. or/7-9
Other: Dosing strategies	11. Dose-Response Relationship, Drug/ or Drug Administration Schedule/ or Pain Management/or Clinical Protocols/ or Breakthrough Pain/ or ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp 12. 3 and (6 or 10) 13. 11 and 12
Other: Risk prediction instruments and diagnostic accuracy	14. Decision Support Techniques/ or "Predictive Value of Tests" or Prognosis or Risk Assessment or Risk Factors or Proportional Hazards Models or "Reproducibility of Results" or "Sensitivity and Specificity" 15. (risk and (predict* or assess*)).mp 16. 14 or 15 17. 3 and (6 or 10) 18. 16 and 17
Other: Risk mitigation strategies	19. Patient Compliance/ or Health Services Misuse/ or Substance Abuse Detection/ or Drug Monitoring/ Drug Overdose/or Contracts/ or Patient Education as Topic/ 20. (urine adj7 (screen\$ or test\$ or detect\$)).mp or (abus\$ or misus\$ or diversion\$ or divert\$).mp or (opioid\$ adj7 (contract\$ or agree\$)).mp or (risk\$ adj7 mitigat\$).mp or ("risk evaluation and mitigation" or "rems").mp 21. 19 or 20 22. 3 and (6 or 10) 23. 23 and 24
Combined searches	Population: chronic pain + Intervention: opioids + Limit to RCTs or controlled observational studies (KQ I-III)
	Population: chronic pain + Intervention: opioids + dosing strategies + Limit to RCTs or controlled observational studies (KQ III)
	Population: chronic pain and/or risk of/current opioid addiction + Intervention: opioids + risk prediction instruments (KQ IVa and IVb)*
	Population: chronic pain or risk of/current opioid addiction + Intervention: opioids + risk mitigation strategies+ Limit to RCTs or controlled observational studies (KQ IVc and IVd)