



## **Evidence-based Practice Center Systematic Review Protocol**

### ***Project Title: Nonopioid Pharmacologic Treatments for Chronic Pain***

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

### **Understanding Chronic Pain**

Chronic pain is typically defined as pain lasting at least 3 to 6 months or that which persists past the time for normal tissue healing.<sup>1</sup> From a strictly biological perspective, pain is activation of the sensory nervous system's nociceptive and hypothalamic-pituitary-adrenal axis.<sup>2</sup> Adding to the complexity of chronic pain are its diverse origins and the subjective experience of a sufferer. Chronic pain can be the result of several issues ranging from a potential underlying medical condition or disease, to inflammation of injured tissue, to neuropathic pain where the patient's central or peripheral nervous system is damaged. The manner in which pain is experienced is more than simply the biological output of an underlying issue. Attitudes, emotional disposition, and belief systems can shape the experience of pain.<sup>1</sup> It is also heavily influenced by extrinsic psychosocial and socioeconomic factors and thus the biopsychosocial impact of chronic pain on the individual is as complex and varied as the disease itself. The physical deficits associated with chronic pain lead to increased medical costs, and reductions in function (disabilities) and quality of life. Psychological and social effects are also common and can manifest in a number of ways, including depression, anxiety, and an inability to fulfill social roles with family, friends, and employers.<sup>1</sup> U.S.-based estimates find that nearly 50 million adults live with chronic pain, contributing to population morbidity and mortality and adding to the economic burden of the healthcare system.<sup>3</sup> Annual healthcare costs due to chronic pain are estimated above \$560 billion, with 2008 costs to federal and state governments alone reaching \$99 billion.<sup>1</sup>

### **Chronic Pain Management**

Pain management is a dynamic process of care for an individual, with a goal of alleviating pain and dysfunction.<sup>4</sup> Understanding pain from the biopsychosocial perspective, its management should be multimodal. The National Pain Strategy (NPS) report recommends a population-based approach which draws upon current scientific evidence.<sup>4</sup> Self-management is often considered an important first step to alleviating chronic pain.<sup>1</sup> While there exist numerous pharmacologic and nonpharmacologic interventions for the treatment of chronic pain, the overview below will focus on pharmacologic treatments.

The most common forms of pharmacologic treatment for pain include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, topical formulations of drugs such as lidocaine, and other drugs such as antiseizure/anticonvulsant medications and antidepressants that are used for moderating pain. Medical marijuana has also been used to treat chronic pain. Pharmacologic treatments can be used individually or in combination and each has potential side effects and contraindications.

Nationally, a concern regarding appropriate use, misuse, and diversion of opioids for treatment of chronic pain has been the subject of numerous scientific and news reports. Opioid

prescriptions for chronic pain have increased substantially in the past 20 years; the number of opioid prescriptions dispensed rose from 76 million in 1999 to over 215 million in 2011, with approximately 35 percent of all opioid overdose deaths in 2017 being attributed to prescription medications.<sup>4,5</sup> However, evidence shows only modest short-term benefits.<sup>6-10</sup> Lack of evidence on long-term effectiveness<sup>8</sup> and serious safety concerns<sup>7</sup> speaks to the need to consider alternative treatments to opioids. The 2016 *CDC Guideline for Prescribing Opioids for Chronic Pain* recommends that nonopioid therapy is preferred for the treatment of chronic pain.<sup>11</sup> To support, update, and expand such guidelines, synthesis of the current state of the science is required to guide clinicians and inform health policy.

## **Rationale for Evidence Review and What this Review Adds**

Requirements in the 2010 Patient Protection and Affordable Care Act led the Department of Health & Human Services to contract with the Institute of Medicine (IOM, now the National Academy of Medicine) to assess the state of the science on pain research, care, and education and formulate recommendations in these key areas.<sup>1,4</sup> Recommendations outlined in the 2011 IOM report have spawned a number of national initiatives to address gaps related to understanding the complexities of pain assessment and management, including the creation of the NPS under the oversight of the Interagency Pain Research Coordinating Committee (IPRCC), and creation of a federal portfolio of existing pain research to help inform additional research needs on pain. Concerns regarding the use of opioids for management of chronic pain are outlined in both the IOM report and the NPS. These initiatives, along with the recent publication of the evidence-based guideline on opioid use for chronic pain by the Centers for Disease Control and Prevention,<sup>11</sup> have prompted additional primary research on alternatives to opioids in managing chronic pain.

Given this context, the complexity of treating chronic pain, and concerns regarding the safety and long-term effectiveness of opioids, there is a real need to fully understand the benefits and harms of nonopioid pharmacologic treatments for chronic pain. The purpose of this report is to evaluate the effectiveness and comparative effectiveness of nonopioid pharmacologic agents, considering the effects on pain, function, quality of life, and adverse events. This review is one of three concurrent systematic reviews on treating chronic pain; other reviews address nonpharmacologic treatments and opioids.

## **II. The Key Questions**

### **Key Question 1. Effectiveness and Comparative Effectiveness**

- a. In patients with chronic pain, what is the effectiveness of nonopioid pharmacologic agents versus placebo for outcomes related to pain, function, and quality of life, after short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration ( $\geq 12$  months)?
- b. In patients with chronic pain, what is the comparative effectiveness of nonopioid pharmacologic agents compared to other nonopioid pharmacologic agents for outcomes related to pain, function, and quality of life, after short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration ( $\geq 12$  months)?

- c. How does effectiveness or comparative effectiveness vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) the dose of medication used, (5) the duration of treatment, and (6) dose titration, including tapering.

## **Key Question 2. Harms and Adverse Events**

- a. In patients with chronic pain, what are the risks of nonopioid pharmacologic agents for harms including overdose, misuse, dependence, withdrawals due to adverse events, and serious adverse events (including falls, fractures, motor vehicle accidents), and specific adverse events, according to drug class?
- b. How do harms vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) the dose of medication used, (5) the duration of treatment, and (6) dose titration, including tapering.

## **PICOTS Inclusion Criteria**

Table 1 in Section IV provides details on the PICOTS inclusion and exclusion criteria. A brief overview of inclusion criteria is listed here:

### **Population(s):**

- For all Key Questions (KQs): Adults (age  $\geq 18$  years) with various types of chronic pain (defined as pain lasting  $>3$  months), including patients with acute exacerbations of chronic pain, pregnant/breastfeeding women, and patients with opioid use disorder
- For KQs 1c, 2b: Subgroups of the above patient populations as defined by specific pain condition (neuropathic pain, musculoskeletal pain, fibromyalgia, inflammatory arthritis, and chronic headache), patient demographics (e.g., age, race, ethnicity, and sex), comorbidities and degree of nociplasticity/central sensitization.

### **Interventions:**

- Oral pharmacologic agents: nonsteroidal anti-inflammatory drugs, acetaminophen, muscle relaxants (including benzodiazepines), antidepressants, and anticonvulsants
- Topical pharmacologic agents: diclofenac, capsaicin, and lidocaine
- Medical cannabis (any formulation)

### **Comparators:**

- For KQ 1a/c and KQ2: Placebo (effectiveness)
- For KQ 1b/c and KQ2: Another included nonopioid pharmacologic agent, different doses, or treatment durations (comparative effectiveness)

### **Outcomes:**

- KQ 1: Pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression)
  - Only validated scales for assessments of pain, function, and quality of life
- KQ 2: For all drug classes: overdose, misuse, dependence, withdrawals due to adverse events, and serious adverse events. Specific adverse events for each drug class, such as gastrointestinal events, cardiovascular events, and liver or kidney-related harms for non-steroidal anti-inflammatory drugs; weight gain, sedation, and cognitive effects for gabapentin and pregabalin, etc.

**Timing:**

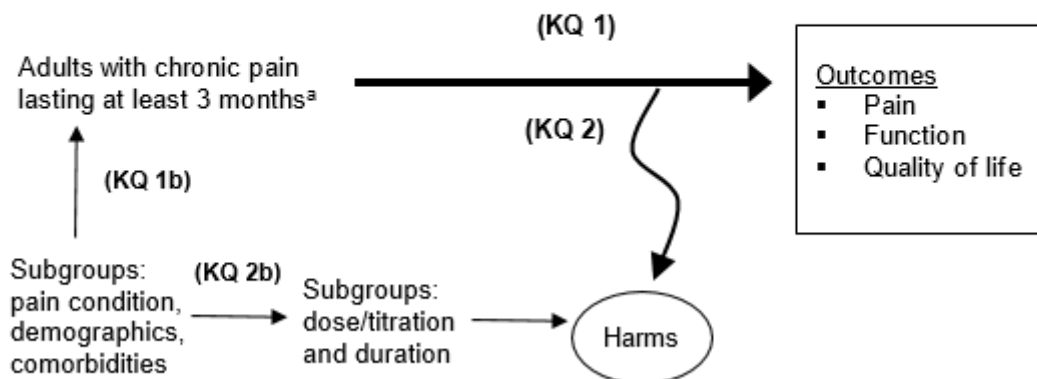
- Short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration ( $\geq 12$  months)
- We will assess available literature to ensure that adequate evidence exists from studies of  $\geq 3$  months' treatment duration. If adequate evidence is not available for this shorter-duration, we will consider adding shorter-duration studies. If high-quality systematic reviews are available covering the scope of the review for shorter duration studies, we will summarize these in this case.

**Settings:**

- Outpatient settings (e.g., primary care, pain clinics, other specialty clinics)

**III. Analytic Framework****Figure 1. Analytic framework for Nonopioid Pharmacologic Treatments for Chronic Pain**

**Interventions:** Nonopioid pharmacologic treatments including: acetaminophen, NSAIDs, topical treatments such as diclofenac, capsaicin and lidocaine, medical marijuana, and antidepressants or anticonvulsants used for chronic pain.



KQ = Key Question

<sup>a</sup>Includes acute exacerbations of chronic pain, pregnant/breastfeeding women, and patients treated with opioids for opioid use disorder

**IV. Methods****Criteria for Inclusion/Exclusion of Studies in the Review**

The criteria for inclusion and exclusion of studies for the systematic review will be based on the Key Questions and are briefly described in the previous PICOTS section and below in Table 1.

**Table 1. PICOTS: Inclusion and exclusion criteria**

PICOTS	Include	Exclude
Populations and Conditions	<ul style="list-style-type: none"> <li>For all KQs: Adults (age ≥18 years) with various types of chronic pain (defined as pain lasting &gt;3 months), including patients with acute exacerbations of chronic pain, pregnant/breastfeeding women, and patients with opioid use disorder</li> <li>For KQs 1b, 2b Specific chronic pain populations: <ul style="list-style-type: none"> <li>Neuropathic</li> <li>Musculoskeletal (low back pain, neck pain and osteoarthritis)</li> <li>Fibromyalgia</li> <li>Sickle cell disease</li> <li>Inflammatory arthritis (e.g., rheumatoid arthritis)</li> <li>Chronic headache<sup>a</sup></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Pain at the end of life</li> <li>Acute pain</li> <li>Pain due to active malignancy</li> <li>Pain due to sickle cell crisis</li> <li>Episodic migraine</li> <li>Undefined mixed pain conditions</li> </ul>
Interventions	<p>Nonopioid pharmacologic treatments given specifically for chronic pain including:</p> <ul style="list-style-type: none"> <li>Oral pharmacologic agents: <ul style="list-style-type: none"> <li>Acetaminophen</li> <li>NSAIDs (e.g., celecoxib, diclofenac, ibuprofen, naproxen)</li> <li>Antidepressant medications specifically used to treat chronic pain; SNRIs (i.e. desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine) and TCAs (e.g., amitriptyline, desipramine, doxepin, imipramine, nortriptyline)</li> <li>Anticonvulsant medications specifically used to treat chronic pain: carbamazepine, gabapentin, oxcarbazepine, pregabalin</li> <li>Muscle relaxants (including benzodiazepines) commonly used to treat chronic pain (e.g., cyclobenzaprine, tizanidine, diazepam)</li> <li>Other: Memantine</li> </ul> </li> <li>Topical pharmacologic agents <ul style="list-style-type: none"> <li>Diclofenac, capsaicin, and lidocaine</li> </ul> </li> <li>Medical cannabis (inhaled, oral, and topical)</li> <li>Phytocannabinoids (plant-derived): THC and CBD</li> <li>Synthetic cannabinoids (FDA-approved): Dronabinol (THC), Nabilone (similar to THC)</li> </ul>	<ul style="list-style-type: none"> <li>Injectable preparations, including biologic drugs, corticosteroids, etc.</li> <li>Other antidepressants not typically used to treat chronic pain, including SSRIs and MAOIs</li> <li>Other antiepileptics not typically used to treat chronic pain, including topiramate, lamotrigine, levetiracetam, phenytoin, valproic acid, zonisamide, tiagabine</li> <li>Drugs used for migraine prophylaxis (e.g., verapamil, beta-blockers) or treating acute migraine (e.g., triptans)</li> <li>Salicylates (topical and oral)</li> <li>Topical menthol preparations</li> <li>Disease-modifying drugs for rheumatoid arthritis (DMARDs, e.g. methotrexate, gold)</li> </ul>
Comparators	<ul style="list-style-type: none"> <li>For KQ 1a/b and 2a/b: Placebo</li> <li>For KQ 1c and 2a/b: Another included nonopioid pharmacologic agent, dose, or treatment duration</li> </ul>	<ul style="list-style-type: none"> <li>Nonpharmacologic treatment (comparison to nonopioids included in review of nonpharmacologic treatments)</li> <li>Opioid treatment</li> </ul>

PICOTS	Include	Exclude
Outcomes	<ul style="list-style-type: none"> <li>Pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life. <ul style="list-style-type: none"> <li>Only validated outcome measures of pain, overall function or disability, and quality of life</li> <li>Secondary outcomes will include depression, anxiety, sleep, and global assessments using validated scales</li> </ul> </li> <li>All drug classes: Withdrawals due to adverse events, serious adverse events, overdose (intentional and unintentional), misuse, and dependence.</li> <li>Key specific adverse events, according to drug class, such as gastrointestinal and cardiovascular events, kidney and liver-related harms with NSAIDs, weight gain, dry mouth/blurred vision, cognitive effects, sedation for gabapentin/pregabalin</li> </ul>	<ul style="list-style-type: none"> <li>Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)</li> </ul>
Timing	<ul style="list-style-type: none"> <li>Short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration (<math>\geq 12</math> months)</li> </ul>	<ul style="list-style-type: none"> <li>Studies or outcomes reported with <math>&lt; 3</math> month duration of treatment<sup>b</sup></li> </ul>
Setting	<ul style="list-style-type: none"> <li>Outpatient settings (e.g., primary care, pain clinics, other specialty clinics, emergency rooms, urgent care clinics)</li> </ul>	<ul style="list-style-type: none"> <li>Addiction treatment settings, inpatient settings</li> </ul>
Study Design	<ul style="list-style-type: none"> <li>Randomized controlled trials</li> <li>High-quality, recent systematic reviews, selecting a limited number that best match the scope of this review<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Observational studies</li> <li>Systematic reviews may be excluded based on currency (e.g., if there is a substantial new body of evidence not included) or relevance (e.g., do not report outcomes or time frames of interest).</li> </ul>

CBD = cannabidiol; FDA = Food and Drug Administration; KQ = Key Question; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; THC = tetrahydrocannabinol

<sup>a</sup> Chronic headache defined as (International Classification of Headache Disorders, 3rd edition definition<sup>12</sup>):

Primary headaches attributed to the headache condition itself, not caused by another disease or medical condition. Chronic headache is defined as 15 or more days each month for at least 12 weeks or history of headache more than 180 days a year.

<sup>b</sup> The Evidence-based Practice Center will assess available literature to ensure that adequate evidence exists from studies of  $\geq 3$  months' treatment duration, and consider adding shorter-duration studies where evidence is inadequate. If high-quality systematic reviews are available covering the scope of the review for shorter duration studies, we will summarize these.

Below are additional details on the scope of this project:

**Study Design:** For all Key Questions, we will include and focus on randomized controlled trials (RCTs) with at least 3 months duration to maintain a manageable scope for this review, recognizing that by definition, chronic pain requires treatments that are effective in the long term, and short-term benefits may not persist. This duration threshold is similar to the duration used in the prior AHRQ systematic review on nonpharmacologic interventions for chronic pain,<sup>13</sup> which included studies with greater than one month of followup after the end of treatment, with most studies involving 6 to 8 weeks of treatment. The Evidence-based Practice Center (EPC) will evaluate the availability and quality of studies with three to six months

duration to determine if an evaluation of studies with shorter durations is needed. As noted above, if there is inadequate evidence found in this window of duration, we will consider inclusion of studies with shorter durations, using existing systematic reviews to summarize the evidence, if possible.

We will evaluate the persistence of benefits or harms by evaluating the three periods identified in the Key Questions (3 to 6 months, 6 to 12 months, and  $\geq 12$  months). We will use existing systematic reviews primarily to screen their included studies to insure we have identified all relevant studies for this review. In the case where a systematic review is recent enough to cover the majority of the available evidence, and evaluates a cohesive group of interventions, outcomes and time frames included here, we will include the review as the primary evidence and supplement with any newer or excluded 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: Electronic searches for evidence will be conducted in January 2019, and will be conducted back to the inception of each database. Electronic searches will be updated after the draft report is submitted, 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<sup>®</sup>, MEDLINE<sup>®</sup>, Embase<sup>®</sup>, PsycINFO<sup>®</sup>, CINAHL<sup>®</sup>, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews will be searched. Search strategies for MEDLINE are available in **Appendix 1**.

Supplemental Evidence And Data for Systematic review (SEADS): Manufacturers of included drugs will be invited to submit information relevant to this review using a Federal Register notification.

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

Process for Selecting Studies: In accordance with the *Methods Guide for Effectiveness and Comparative Effectiveness Review*,<sup>14</sup> we will use the pre-established criteria above to screen citations (titles and abstracts) identified through our searches to determine eligibility for full-text review. To ensure accuracy, any citation deemed not relevant for full-text review will be reviewed by a second researcher. All citations deemed potentially eligible for inclusion by at least one of the reviewers will be retrieved for full-text screening. Each full-text article will be independently reviewed for eligibility by two team members. Any disagreements will be resolved by consensus.

### **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.

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

RCTs will be assessed based on criteria established in the *Cochrane Handbook for Systematic Reviews of Interventions (Chapter 8.5 Risk of Bias Tool)*,<sup>15</sup> and principles for appraisal as developed by the Cochrane Back and Neck Group.<sup>16</sup> Methods from the *Methods Guide for Effectiveness and Comparative Effectiveness Review* will be used in concordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions.<sup>14,17</sup> Based on the risk of bias assessment, individual included studies will be rated as being “good,” “fair,” or “poor” quality. Studies included in prior systematic reviews conducted by our EPC that are relevant to this review were assessed using the methods of the U.S. Preventive Services Task Force<sup>18</sup> and the Drug Effectiveness Review Project,<sup>19</sup> which are based on criteria very similar to the Cochrane methods proposed here. We will re-evaluate the quality assessments of any studies rated poor quality in the prior reviews to insure consistency with methods used here.

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.

### **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 prior Drug Effectiveness Review project and Agency for Healthcare Research and Quality reviews as well as new studies identified in current searches.

Data will be qualitatively summarized in tables, using ranges and descriptive analysis and interpretation of the results. The magnitude of effects for pain and function will be classified using the same system as in the 2018 AHRQ noninvasive treatment for chronic pain review,<sup>13</sup> recognizing that small effects using this system may not meet standard thresholds for clinically meaningful effects. A *small/slight* effect was defined for pain as a mean between-group difference following treatment of 5 to <10 points on a 0 to 100-point visual analog scale (VAS), 0.5 to 1.0 points on a 0 to 10-point numeric rating scale, or equivalent; for function as a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI) or 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent; and for any outcome as a standardized mean difference (SMD) of 0.2 to 0.5. A *moderate* effect was defined for pain as a mean difference of 10 to 20 points on a 0 to 100-point VAS, for function as a mean difference of 10 to 20 points on the ODI or 2 to 5 points on the RDQ, and for any outcome as an SMD of 0.5 to 0.8. Large/substantial effects were defined as greater than *moderate* (>20 points). We will apply similar methodology to outcomes measures. The clinical relevance of effects classified as small/slight might vary for individual patients depending on preferences, baseline symptom severity, harms, cost, and other factors.

Meta-analyses, using random effects models, will be conducted to summarize data and obtain more precise estimates where there are at least three studies reporting outcomes that 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 dosing strategies, and durations. Meta-regression may be conducted to explore statistical heterogeneity using additional variables for methodological or other characteristics (e.g., quality, randomization or blinding, outcome definition and ascertainment) given a large enough number of studies (e.g. at least six to ten studies for continuous variables and four studies for categorical variables).<sup>20</sup>

Results will be presented as structured by the Key Questions, and any prioritized outcomes will be presented first.

### **Grading the Strength of Evidence for Major 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 *Methods Guide for Effectiveness and Comparative Effectiveness Review*.<sup>21</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.

## **Assessing Applicability**

Applicability will be assessed in accordance with the AHRQ's Methods Guide,<sup>21,22</sup> which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different patients and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the studies<sup>23</sup>. For example, exclusion of chronic pain patients with psychiatric comorbidities reduces applicability to clinical practice since many patients with chronic pain have such comorbidities, and may respond more poorly to treatment. Similarly, trials that use placebo or active run-in periods evaluate highly selected populations who tolerated and responded well to the study intervention or who would have responded to placebo, rather than the general population of chronic pain patients being considered to the intervention. Factors that may affect applicability which we have identified a priori include eligibility criteria and patient factors (e.g., demographic characteristics, duration or severity of pain, underlying pain condition, presence of medical and psychiatric comorbidities, event rates and symptom severity in treatment and control groups), intervention factors (e.g., dose and duration of therapy, intensity and frequency of monitoring, level of adherence support, use of co-interventions), comparisons (e.g., type of comparator, effectiveness and feasibility of active comparators), outcomes (e.g., use of unvalidated or nonstandardized outcomes, measurement of short-term or surrogate outcomes), settings (e.g., primary care vs. specialty setting, country), and study design features (e.g., use of run-in periods or enriched enrollment randomized withdrawal design) relevant to applicability. We will use this information to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

## V. References

1. Institute of Medicine Committee on Advancing Pain Research C, Education. The National Academies Collection: Reports funded by National Institutes of Health. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): National Academies Press (US); 2011. Doi:10.17226/13172. PMID: 22553896.
2. Gatchel RJ, McGeary DD, McGeary CA, et al. Interdisciplinary chronic pain management: past, present, and future. *The American psychologist*. 2014 Feb-Mar;69(2):119-30. doi: 10.1037/a0035514. PMID: 24547798.
3. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. *MMWR. Morbidity and mortality weekly report*. 2018;67(36):1001-6. doi: 10.15585/mmwr.mm6736a2. PMID: 30212442.
4. National Pain Strategy Task Force, Interagency Pain Research Coordinating Committee (IPRCC). National Pain Strategy: A Comprehensive Population Health-Level Strategy for Pain. National Institutes of Health (NIH); 2015. [https://iprcc.nih.gov/sites/default/files/HHSNational\\_Pain\\_Strategy\\_508C.pdf](https://iprcc.nih.gov/sites/default/files/HHSNational_Pain_Strategy_508C.pdf) Accessed February 1, 2019.
5. Centers for Disease Control and Prevention. Prescription Opioid Data. 2018. <https://www.cdc.gov/drugoverdose/data/prescribing.html>. Accessed February 1, 2019.
6. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol Drug Saf*. 2009;18(12):1166-75. doi: 10.1002/pds.1833. PMID: 19718704
7. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb Mortal Wkly Rep*. 2011 Nov 4;60(43):1487-92. PMID: 22048730.
8. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4):276-86. doi: 10.7326/M14-2559. PMID: 25581257.
9. Olsen Y, Daumit GL, Ford DE. Opioid prescriptions by U.S. primary care physicians from 1992 to 2001. *J Pain*. 2006 Apr;7(4):225-35. doi: 10.1016/j.jpain.2005.11.006. PMID: 16618466.
10. Sullivan MD, Edlund MJ, Fan M-Y, et al. Trends in use of opioids for non-cancer pain conditions 2000--2005 in commercial and Medicaid insurance plans: the TROUP study. *Pain*. 2008;138(2):440-9.
11. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA*. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464. PMID: 26977696.
12. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2013 Jan;38(1):1-211. doi: 10.1177/0333102417738202. PMID: 29368949.
13. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Rockville, MD: Agency for Healthcare Research and Quality; 2018. PMID: 30179389.
14. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiology and drug safety*. 2009;18(12):1166-75.
15. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. The Cochrane Collaboration; March 2011. <http://handbook-5-1.cochrane.org/> Accessed February 1, 2019.
16. Furlan AD, Malmivaara A, Chou R, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)*. 2015 Nov;40(21):1660-73. doi: 10.1097/BRS.0000000000001061. PMID: 26208232.
17. Viswanathan M, Patnode CD, Berkman ND, et al. Assessing the risk of bias in systematic reviews of health care interventions. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research and Quality; Dec 13, 2017.
18. US Preventive Services Task Force Procedure Manual. Rockville, MD: Agency for Healthcare Research and Quality; October 2015. <https://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual>. Accessed February 1, 2019.
19. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the Drug Effectiveness Review Project. *BMC Med Res Methodol*. 2012 Sep 12;12:140-. doi: 10.1186/1471-2288-12-140. PMID: 22970848.

20. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1187-97. doi: 10.1016/j.jclinepi.2010.08.010. PMID: 21477993.
21. Agency for Healthcare Research and Quality. Methods guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research Quality: 10(13)-EHC063-EF APN; Jan 2014. <https://effectivehealthcare.ahrq.gov/topics/ceer-methods-guide/overview>.
22. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *Journal of clinical epidemiology*. 2011 Nov;64(11):1198-207. doi: 10.1016/j.jclinepi.2010.11.021. PMID: 21463926.
23. Murad MH, Katabi A, Benkhadra R, et al. External validity, generalisability, applicability and directness: a brief primer. *Evidence-based medicine*. 2018;23(1):17-9.

## **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. 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 Agency for Healthcare Research and Quality Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **XI. Peer Reviewers**

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

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

## **XII. EPC Team Disclosures**

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

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

This project was funded under Contract No. HHSA 290-2015-00009-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## **XIV. Registration**

This protocol will be registered in the International Prospective Register of Systematic Reviews (PROSPERO).