



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Systematic Review Update - Noninvasive Nonpharmacologic Treatment for Chronic Pain*

I. Background and Objectives for the Systematic Review

Nature and Burden of Chronic Pain

Chronic pain, often defined as pain lasting longer than 3 to 6 months or persisting past the normal time for tissue healing,¹ is a monumental public health challenge. It affects millions of adults in the United States, with a conservative annual cost estimated at \$560 billion to \$635 billion.¹ In addition to personal and health system expenditures, chronic pain substantially impacts physical and mental functioning, productivity, and quality of life, as well as relationships with family; it is the leading cause of disability and is often refractory to treatment.^{2,3} Nervous system changes that occur with chronic pain, combined with its psychological and cognitive impacts, have led to conceptualization of chronic pain as a distinct disease entity.¹ This multifaceted disease is influenced by multiple factors (e.g., genetic, central nervous system, psychological, and environmental factors), with complex interactions, making assessment and management a challenge. A number of characteristics influence the development of and response to chronic pain, including sex, age, presence of comorbidities, and psychosocial factors. For example, women report chronic pain more frequently than do men, are at higher risk for some conditions such as fibromyalgia,¹ and may respond differently than men. Older adults are more likely to have comorbidities and are more susceptible to polypharmacy, impacting choices and consequences of therapies. Pain is greatly influenced by psychosocial factors, which may predict who will develop chronic disabling pain as well as treatment response. Therefore, chronic pain is best understood from a biopsychosocial perspective. This means that consideration of psychological and social factors as well as underlying biological mechanisms and physical manifestations of chronic pain is necessary for effective management. Musculoskeletal pain, particularly related to joints and the back, is the most common single type of chronic pain.¹ This systemic review will update our previous 2018 review⁴ which focused on five common chronic pain conditions: low back pain, neck pain, osteoarthritis, fibromyalgia, and headache.

Management of Chronic Pain

The overarching goal of chronic pain management is to relieve pain and improve function. The National Pain Strategy (NPS) report recommends that management be integrated, multimodal, interdisciplinary, evidence-based, and tailored to individual patient needs.⁵ In addition to addressing biological factors when known, it is thought that optimal management of chronic pain also addresses psychosocial contributors to pain, while taking into account individual susceptibility and treatment responses. Self-care is an important part of chronic pain management. At the same time, the NPS points to the

“dual crises” of chronic pain and opioid dependence, overdose, and death as providing important context for consideration and implementation of chronic pain management strategies. A vast array of pharmacologic and nonpharmacologic treatments is available for management of chronic pain. An overview of these interventions is briefly presented below.

Pharmacologic Treatment

Pharmacologic treatments for chronic pain may include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, antiseizure/anticonvulsant medications, antidepressants, muscle relaxants and opioids. Medical marijuana has been also used for management of chronic pain. Pharmacologic treatments may be used alone or in combination, and may be used in combination with nonpharmacologic treatment. Each pharmacologic treatment has potential side effects and contraindications.

Noninvasive, Nonpharmacologic Treatment

Noninvasive methods considered for this report will include exercise (including aspects of physical therapy), mind-body practices (Yoga, Tai Chi, Qigong), psychological therapies (cognitive-behavioral therapy, biofeedback, relaxation techniques, acceptance and commitment therapy), interdisciplinary rehabilitation (including functional restoration), mindfulness practices (meditation, mindfulness-based stress reduction practices), spinal manipulation (e.g., chiropractic or osteopathic manipulation), acupuncture, and physical modalities (traction, ultrasound, transcutaneous electrical nerve stimulation [TENS], low level laser therapy, interferential therapy, superficial heat or cold, bracing for knee, back or neck, electro-muscular stimulation, and magnets), and acupuncture. Across many chronic pain conditions, exercise is commonly recommended.

Rationale for Evidence Review Update

Requirements in the *2010 Patient Protection and Affordable Care Act* led the Department of Health & Human Services (HHS) to contract with the Institute of Medicine (IOM) to assess the state of the science on pain research, care, and education and formulate recommendations in these key areas.^{1,5} 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. The recent publication of evidence-based guidelines on opioid use for chronic pain by the Centers for Disease Control (CDC),¹² which includes a recommendation on the preferred use of non-opioid treatment over opioid therapy, has prompted additional primary research on alternative methods of managing chronic pain. Both the IOM report and the NPS describe the need for evidence-based strategies for the treatment of chronic pain that address the biopsychosocial nature of this disease, including nonpharmacologic treatment. These initiatives, and others, speak to the importance of understanding current evidence on noninvasive nonpharmacologic treatment of chronic pain. Given this need and widespread concern regarding opioid use and misuse outlined in recent guidelines and

reviews, the impact of this update report is potentially far-reaching. The evidence synthesized in this review update together with the other two commissioned reviews will help inform guidelines and health care policy related to use of noninvasive, nonpharmacologic, and pharmacologic treatments for management of common chronic pain conditions. The report update will provide additional evidence to address gaps in evidence identified in the previous report and thus some of the needs described in the NPS⁵ and IOM¹ reports and others for evidence regarding treatment options. The update review may also provide additional insights into persistent research gaps related to use of noninvasive, nonpharmacologic alternatives for treating chronic pain.

II. The Key Questions

The final Key Questions for this update review are as follows:

1. In adults with chronic low back pain:
 - a. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
 - b. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with pharmacologic therapy (e.g., NSAIDs, acetaminophen, antiseizure medications, antidepressants)?
 - c. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with exercise?
2. In adults with chronic neck pain:
 - a. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
 - b. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with pharmacologic therapy?
 - c. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with exercise?
3. In adults with osteoarthritis-related pain:
 - a. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
 - b. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with pharmacologic therapy?
 - c. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with exercise?
4. In adults with fibromyalgia:
 - a. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
 - b. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with pharmacologic therapy?

- c. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with exercise?
5. In adults with chronic tension headache:
 - a. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
 - b. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with pharmacologic therapy?
 - c. What are the benefits and harms of noninvasive nonpharmacologic therapies compared with biofeedback?
6. Do estimates of benefits and harms differ by age, sex, presence of comorbidities (e.g., emotional or mood disorders) or degree of nociplasticity/central sensitization?

PICOTS Inclusion Criteria

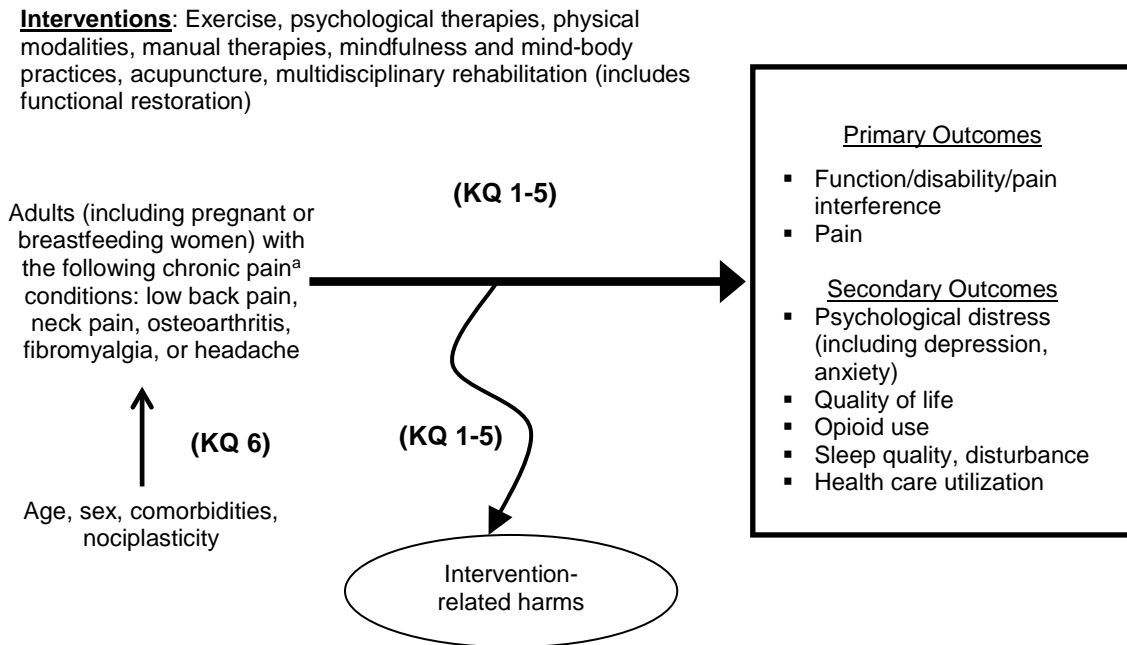
The PICOTS for the update review will remain the same with two changes: 1) Pregnant or breastfeeding women with chronic pain prior to pregnancy will be included. Pregnancy-related pain (e.g. back pain or pelvic pain) will be excluded; 2) inclusion of additional pharmacologic comparators (topical agents, medical cannabis, muscle relaxants). A brief overview of the PICOTS inclusion criteria is provided here:

- **Population(s):** Adults (including pregnant or breastfeeding women) with the following chronic pain (defined as pain lasting 12 weeks or longer or pain persisting past the time for normal tissue healing) conditions specified in the Key Questions:
 - Key Question 1: Nonradicular chronic low back pain
 - Key Question 2: Chronic neck pain without radiculopathy or myelopathy
 - Key Question 3: Pain related to primary or secondary osteoarthritis
 - Key Question 4: Fibromyalgia
 - Key Question 5: Primary chronic tension headache (defined as 15 or more headache days per month for at least 3 months)
 - Key Question 6: Patients with any of the five chronic pain conditions.
- **Interventions (All Key Questions):**
 - Exercise
 - Psychological therapies
 - Physical modalities
 - Manual therapies
 - Mindfulness practices
 - Mind-body practices
 - Acupuncture
 - Multidisciplinary/interdisciplinary rehabilitation (including functional restoration training)
- **Comparators:**

- **For all Key Questions, subquestion “a”**
 - Sham treatment
 - Waitlist
 - Usual care
 - Attention control
 - No treatment
- **For all Key Questions, subquestion “b”**
 - Common nonopioid pharmacologic therapy used for chronic pain (NSAIDs, acetaminophen, antiseizure medications, antidepressants, muscle relaxants (including benzodiazepines) topical agents, (diclofenac, lidocaine capsaicin)
 - Medical marijuana (any formulation)
 - Opioid analgesics
- **Key Questions 1-4, 6, subquestion “c”:** Exercise
- **Key Question 5, 6, subquestion “c”:** Biofeedback.
- **Outcomes:**
 - Primary efficacy outcomes (in priority order); we will focus on outcomes from validated measures
 - Function/disability/pain interference
 - Pain
 - Harms and adverse effects
 - Secondary outcomes
 - Psychological distress (including depression and anxiety)
 - Quality of life
 - Opioid use
 - Sleep quality, sleep disturbance
 - Health care utilization.
- **Timing:**
 - Duration of followup: short term (up to 6 months), intermediate term (6-12 months) and long term (at least 1 year); we will focus on longer-term (>1 year) effects where possible
 - Studies with <1 month followup after treatment will be excluded.
- **Settings:**
 - Any nonhospital setting or setting of self-directed care
 - Exclusions: Hospital care, hospice care, emergency department care.

III. Analytic Framework

Figure 1. Analytic framework for noninvasive nonpharmacologic treatment for chronic pain



KQ=Key Question

^aChronic pain is defined as pain lasting ≥ 12 weeks or pain persisting past the normal time for tissue healing.

IV. Methods

A. 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	Inclusion	Exclusion
Patients	<p>General Inclusion Criteria</p> <ul style="list-style-type: none"> Adults with the following chronic pain (defined as pain lasting 12 weeks or longer or pain persisting past the time for normal tissue healing) conditions: low back pain, neck pain, osteoarthritis pain, fibromyalgia, or tension headache. Pregnant or breastfeeding women who have a history of chronic pain prior to pregnancy <p>KQ1: Low back pain</p> <ul style="list-style-type: none"> Adults with chronic, nonradicular low back pain <p>KQ2: Neck pain</p> <ul style="list-style-type: none"> Adults with chronic neck pain <p>KQ3: Osteoarthritis</p> <ul style="list-style-type: none"> Adults with osteoarthritis-related pain (primary or secondary osteoarthritis) of the hip, knee or hand <p>KQ4: Fibromyalgia</p> <ul style="list-style-type: none"> Adults with fibromyalgia <p>KQ5: Headache</p> <ul style="list-style-type: none"> Adults with primary chronic tension headache (International Classification of Headache Disorders, 3rd edition definition). <ul style="list-style-type: none"> Primary headaches are attributed to the headache condition itself, not headache caused by another disease or medical condition. Tension headaches are the most common. 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. 	<p>General Exclusion Criteria</p> <ul style="list-style-type: none"> Acute pain Children (<18 years), pregnant or breastfeeding women with pregnancy-related back or pelvic pain or who do not have chronic pain prior to pregnancy; Patients with chronic pain related to “active” cancer, infection, inflammatory arthropathy, <90% of study sample has the defined condition of interest or <90% received the treatment(s) of interest Treatment for addiction Pain at the end of life Neuropathic pain <p>KQ1: Low back pain</p> <ul style="list-style-type: none"> Patients with radiculopathy Low back pain associated with severe or progressive neurological deficits Failed back surgery syndrome <p>KQ2: Neck pain</p> <ul style="list-style-type: none"> Patients with radiculopathy or myelopathy Traumatic spinal cord injury Neck pain associated with progressive neurological deficit, loss of strength <p>KQ3: Osteoarthritis</p> <ul style="list-style-type: none"> Other types of arthritis (e.g., rheumatoid) Patients with joint replacement <p>KQ4: Fibromyalgia</p> <ul style="list-style-type: none"> Conditions with generalized pain not consistent with fibromyalgia Systemic exertion intolerance disease, (myalgic encephalomyelitis/chronic fatigue syndrome) Somatization disorder (Briquet’s syndrome) <p>KQ5: Headache</p> <ul style="list-style-type: none"> Migraine headache Mixed headache (also known as coexistent tension and migraine headache, chronic daily headache, transformed migraine) Trigeminal neuralgia Cluster headache Secondary headache types as defined in <i>The International Classification of Headache Disorders</i>, 3rd edition¹⁵ (i.e., headaches due to an underlying pathology such as cancer, prior medical procedures, temporomandibular joint disorders, neck pathology, cervicogenic headache, and medication over-use headache) Traumatic brain injury

PICOTS	Inclusion	Exclusion
Interventions	<p>All KQs:</p> <ul style="list-style-type: none"> • Exercise (exercise as part of physical therapy, supervised exercise, home exercise, group exercise, formal exercise program) • Psychological therapies (cognitive and/or behavioral therapy, biofeedback, relaxation training) • Physical modalities (traction, ultrasound, transcutaneous electrical nerve stimulation, low level laser therapy, interferential therapy, electro-muscular stimulation diathermy, superficial heat or cold, bracing for knee, back, neck, hand and magnets) • Manual therapies (musculoskeletal manipulation, massage) • Mindfulness practices (meditation, mindfulness-based stress reduction practices) • Mind-body practices (yoga, tai chi, qigong) • Acupuncture • Multidisciplinary/interdisciplinary rehabilitation^a 	<p>All KQs:</p> <ul style="list-style-type: none"> • Invasive nonsurgical treatments (e.g., injections, nerve block, spinal cord stimulators, parenterally-administered medications) • Surgical interventions (including minimally invasive surgical interventions) • Diet interventions or dietary supplementation • Studies evaluating incremental value of adding a noninvasive nonpharmacologic intervention to another noninvasive nonpharmacologic intervention • Self-management interventions or programs, self-management education programs • Others not listed for inclusion
Comparators	<p>All KQs, subquestion a</p> <ul style="list-style-type: none"> • Sham treatment • Waitlist • Usual care • No treatment • Attention control intended to control for nonspecific effects (e.g., time, attention, expectations) <p>All KQs subquestion b</p> <ul style="list-style-type: none"> • Commonly used nonopioid pharmacologic therapy used to treat chronic pain (NSAIDs, acetaminophen, anti-seizure medications, antidepressants (SNRIs, TCAs), muscle relaxants (including benzodiazepines)) • Topical agents (lidocaine, diclofenac, capsaicin) • Medical cannabis (inhaled, oral, topical); phytocannabinoids (plant derived, THC and CBD); FDA approved synthetic cannabinoids (Dronabinol [THC], Nabilone [similar to THC]) • Opioid analgesics <p>KQs 1-4, 6 subquestion c</p> <ul style="list-style-type: none"> • Exercise^b <p>KQ 5, 6 subquestion c</p> <ul style="list-style-type: none"> • Biofeedback^c 	<p>All KQs:</p> <ul style="list-style-type: none"> • Supplements (e.g., glucosamine, chondroitin, d-ribose, herbal or homeopathic treatments) • Invasive nonsurgical treatments (e.g., injections, nerve block, spinal cord stimulators, parenterally-administered medications) • Antidepressants not typically used for chronic pain including SSRIs and MAOIs • Anti-seizure medications not typically used to treat chronic pain including topiramate, lamotrigine, levetiracetam, phenytoin, valproic acid, zonisamide, tiagabine • Surgical interventions (including minimally invasive surgical interventions) • Studies evaluating incremental value of adding a noninvasive nonpharmacologic intervention to another noninvasive, nonpharmacologic intervention • Comparisons within nonpharmacologic intervention types (e.g., comparisons of different types of exercise with each other, different types of massage with each other) • Corticosteroids, biologic drugs • Salicylates (oral and topical) • Topical menthol preparations • Others not listed for inclusion

PICOTS	Inclusion	Exclusion
Outcomes	<p>All KQs: Primary efficacy outcomes; we will focus on outcomes from validated measures for</p> <ul style="list-style-type: none"> • Function/disability/pain interference^d • Pain^d <p>Harms and Adverse effects</p> <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Psychological distress (including measures of depression and anxiety) • Quality of life • Opioid use • Sleep quality, sleep disturbance • Health care utilization 	<p>All KQs:</p> <ul style="list-style-type: none"> • Intermediate outcomes (e.g., biomarkers for inflammation) • Other nonclinical outcomes
Studies	Randomized controlled trials or high quality systematic reviews of randomized controlled trials published in English; cross-over trials with random assignment of initial treatment will be considered.	<p>All KQs:</p> <ul style="list-style-type: none"> • Studies reporting on intermediate outcomes only • Nonrandomized studies • Abstracts, editorials, letters, conference proceedings • Duplicate publications of the same study that do not report on different outcomes • Single site reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Indirect comparisons • Studies with fewer than 15 patients per treatment arm • Systematic reviews on treatment of chronic neck pain, fibromyalgia, chronic headache, or osteoarthritis that are of low methodological quality. Those that do not report outcomes or time frames of interest may be excluded. Systematic reviews may be excluded based on currency or relevance (e.g., if there is a substantial new body of evidence reflected in a later review). • Observational studies
Setting(s)	Any nonhospital setting or in self-directed care	<ul style="list-style-type: none"> • Hospital care, hospice care, emergency department care
Timing	Duration of followup: short term (1 to <6 months), intermediate term (≥6 to <12 months) and long term (≥12 months); focus on longer term (≥12 month) effects. Trials lasting ≥6 months that include a supervised intervention followed by continued home treatment as part of the intervention will be included even though the only followup occurs directly after the intervention.	<ul style="list-style-type: none"> • Studies with <1 month followup after treatment

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

^a Multidisciplinary rehabilitation (MDR) (also known as interdisciplinary rehabilitation), is defined as a coordinated program with biopsychosocial treatment components (e.g., exercise therapy and cognitive-behavioral therapy) provided by professionals from at least two different specialties. Functional restoration training is included as part of MDR

^b Different forms of exercise will not be compared to each other. Exercise will be compared with nonexercise interventions for low back pain, neck pain, fibromyalgia and osteoarthritis

^c Different forms of biofeedback will not be compared to each other. Biofeedback will be compared with the noninvasive interventions for chronic headache

^d The magnitude of effects for pain and function will be classified using the same system as in the 2018 AHRQ-funded noninvasive treatment for chronic pain review. (See methods section.)

Below are additional details on the scope of this project:

Study Designs: The focus of this review is on randomized controlled trials (RCTs) reporting on longer-term outcomes (at least one month post intervention) that otherwise meet our PICOTS criteria. We will focus on RCTs and evaluate references of systematic reviews against our inclusion criteria, directly incorporating new primary trials into our review; we will not use previous reviews as primary evidence. Data from studies used in our previous systematic review will be combined with data from new primary trials identified via our searches and we will update or perform meta-analyses if appropriate. We will assess strength of evidence and draw conclusions based on the totality of evidence available. The bibliographies of recent, relevant systematic reviews will be hand searched to identify potentially relevant trials; trials identified will be screened for eligibility using the same criteria as for trials identified through literature searches. We will exclude cohort studies, case-control studies, case reports, and case series.

Non-English Language Studies: We will restrict inclusion to English language articles, given the large volume of literature written in English on this topic. We will keep track of studies not written in English that would otherwise meet inclusion criteria to provide insight regarding possible language bias.

Conference Abstracts: Studies only published as conference abstracts will be excluded, but we will review studies that otherwise meet inclusion criteria to help assess for potential publication bias.

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

Publication Date Range: Searches will be conducted for studies published subsequent to our 2018 report and will include citations from September 1, 2017 through December 11, 2018. For inclusion of topical agents and marijuana as comparators, citations from the 2018 review search will be re-evaluated to identify relevant studies and includable studies will be combined with those from the updated search for this review.

Electronic literature searches will be updated while the draft report is posted for public comment 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®, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov will be searched to capture both published and gray literature. These were considered to be the most relevant databases for the study types, pain conditions, and treatments to be reviewed and most likely to yield a high proportion of includable studies. The Ovid MEDLINE search strategy is found in Appendix A.

Supplemental Evidence and Data for Systematic Reviews (SEADS) As there are multiple manufacturers/sources for many of the device/interventions we will be examining in this review, it was determined that a Federal Register notice would be most appropriate. A SEADS portal will be available.

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 for Effectiveness and Comparative Effectiveness Reviews*.¹⁶ 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, submission through the SEADS portal or response to Federal Register notice. Any disagreements will be resolved by consensus. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

C. Data Abstraction and Data Management

Using established templates from the 2018 review, data from new studies will be abstracted into categories that include but are not limited to: study design, year, setting, country, sample size, eligibility criteria, attrition, population and clinical characteristics (including age, sex, comorbidities, diagnostic classifications/information, pain characteristics (e.g. degree of nociplasticity), sociodemographic factors), intervention characteristics (including the type, number, intensity, duration of, and -adherence to treatments), comparator characteristics, and results including harms. Information relevant for assessing applicability will be abstracted, including the characteristics of the population, interventions and the number of patients enrolled relative to the number assessed for eligibility.

All extracted study data will be verified for accuracy and completeness by a second team member.

We recognize that there is heterogeneity within each of the included conditions as well as within each of the included interventions.

- Regarding conditions, we will abstract details for each primary condition including diagnostic criteria used and stratify as possible (e.g., by etiology of low back pain or affected area for osteoarthritis such as hip or knee). To the extent possible, we will abstract data on concomitant pain in areas other than the primary condition under study and the degree of nociplasticity/central sensitization of pain. It is likely that trials vary in regard to the degree to which characteristics of a given condition or presence and characteristics of pain are specified. In some instances, there may not be validated or reliable methods for diagnosing a specific underlying condition.
- Regarding interventions, the type, duration, frequency, components, adherence to the intervention, setting, and other pertinent details will be abstracted and considered. To the extent that the interventions are distinct we will separate them out for analysis and reporting.
- Regarding exercise, we realize that there is likely substantial diversity in the types and delivery of exercise programs. Our focus will be on formal exercise programs and we will abstract details of the type and implementation, and stratify by such factors to the extent possible.
- We recognize that interventions such as formal exercise programs may include components of other interventions (e.g., cognitive behavioral therapy). In such cases, if the additional intervention is a minor component of the overall intervention, we will include the study and focus on the primary intervention. As appropriate, sensitivity analyses may be performed to elucidate differences between studies that do and do not contain the additional, minor component. Our intention is to focus on single active interventions and comparators.
- We recognize that patients will likely have concomitant pharmacologic treatments. We will abstract details of such cointerventions.

D. Assessment of Methodological Risk of Bias of Individual Studies

The predefined criteria used for the 2018 report will be used to assess the quality of included studies. We will focus on studies with the least potential for bias and the fewest limitations. Primarily RCTs will be assessed based on criteria and methods established in the *Cochrane Handbook for Systematic Reviews of Interventions (Chapter 8.5 Risk of Bias Tool)*,¹⁷ and precepts for appraisal developed by the Cochrane Back and Neck Group.¹⁸ These criteria and methods will be used in concordance with the approach recommended in the chapter, *Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions*,¹⁹ from the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.¹⁶ Based on the risk of bias assessment, individual included studies will be rated as being “good,” “fair,” or “poor” quality.

Studies rated “good” are considered to have the least risk of bias, and their results are considered valid. Good-quality studies employ valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline

characteristics in different treatment groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis).

Studies rated “fair” are 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” 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. 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. Studies rated as being poor in quality a priori were not excluded, but 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 discussion and consensus.

E. Data Synthesis

We will incorporate data from new trials to existing evidence tables identifying the study and patient characteristics (as discussed above), results of interest, and quality ratings for all included studies, and summary tables and/or figures 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. Studies with the least risk of bias will be summarized separately and compared with summarized results from poorer-quality studies.

Findings will be synthesized qualitatively (based on ranges and descriptive analysis, with interpretation of results) and quantitatively (meta-analysis) when appropriate. For synthesis, we will again prioritize outcomes for function, pain and harms based on input received from the Key Informants and Technical Expert Panel for the 2018 report. Based on input from stakeholders, improvement in function was prioritized as the most important outcome. Only validated measures for function and pain will be reported. There is overlap between functional outcomes measures and quality of life measures. Short-Form 36 (SF-36) and EuroQoL-5 Dimensions (EQ-5D) are two such outcome measures and they were categorized as quality of life measures for previous report and will be categorized as such for the update as well. Where data are provided, we will compare proportions of patients who experience a clinically important improvement in pain

or function for treatments/comparators. This provides valuable insight regarding clinically important improvement that may be more clinically relevant to understanding intervention benefits. Where mean improvements are reported, the magnitude of effects for pain and function will be classified using the same system as in the 2018 AHRQ-funded noninvasive treatment for treatment for chronic pain review⁴ 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-point difference 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. We will apply similar methodology to outcomes measures for the other conditions. 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 from the 2018 report will be updated and new analyses conducted to summarize data and obtain more precise estimates on the primary outcomes of function and pain for which studies are homogeneous enough to provide a meaningful combined estimate. The feasibility of a quantitative synthesis will depend on trial size, the number and completeness of reported outcomes, and a judgment of adequate homogeneity among the reported results.¹⁶ In general, pooling would be considered if at least two trials are available for a specific comparison and primary outcome. To determine whether meta-analysis could be meaningfully performed, study quality, heterogeneity across studies with regard to patient population, intervention and outcomes, and sample size will be considered as will statistical tests for heterogeneity. Random effects across studies are assumed and if estimates across studies vary widely, profile likelihood methods will be used to combine studies to account for uncertainty across them and provide more conservative estimates.²⁰⁻²² Primary analyses will be stratified by disease type, intervention, control group (usual care, exercise, or pharmacologic treatment) and length of followup (short, intermediate, and long term). To the extent that the interventions within a given category are distinct we will separate them out for analysis and reporting. We will perform sensitivity and subgroup analyses based on specific interventions (e.g., type of acupuncture, type of exercise, intervention intensity etc.) and control types (as described above) and by excluding outlying studies and studies rated as poor. Meta-regression may be conducted to explore statistical heterogeneity using patient demographics and characteristics, comorbidities, treatment features (including specific techniques and number and intensity of treatments) and dosing strategies and additional variables on methodological or other characteristics (e.g., quality, randomization or blinding,

outcome definition and ascertainment, publication date) given the availability of at least six to ten studies for continuous variables and four studies for categorical variables.²³

Results will be presented as structured by the Key Questions, and any prioritized outcomes will be presented first. For some conditions, such as osteoarthritis, results will be organized by affected region (e.g., knee, hip, hand).

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

The strength of evidence for each body of evidence (based on the Key Question, condition of interest, and intervention, comparator, and outcome) will be initially assessed by one researcher with experience in determining strength of evidence for each primary clinical outcome by following the principles for adapting GRADE (Grading of Recommendations Assessment, Development and Evaluation), outlined in the AHRQ methods guide.¹⁶ The initial assessment will be independently reviewed by at least one other experienced investigator.

Prioritization of primary outcomes reflected in the PICOTS table is based on input from the Key Informants for the 2018 review in combination with team expertise. The listed outcomes were considered to be most clinically relevant and important to patients. We incorporated input from the 2018 report's Technical Expert Panel on clinically important outcomes for each condition to further prioritize functional and pain outcomes and harms for synthesis and strength of evidence determination.

In determining the strength of a body of evidence for each prioritized primary or safety outcome, the following domains are evaluated:

- Study limitations: the extent to which studies reporting on a particular outcome are likely to be protected from bias. The aggregate risk of bias across individual studies reporting an outcome is considered; graded as low, medium, or high level of study limitations
- Consistency: the extent to which studies report the same direction or magnitude of effect for a particular outcome; graded as consistent, inconsistent, or unknown (in the case of a single study)
- Directness: generally reflects whether the outcome is directly or indirectly related to health outcomes of interest. Patient centered outcomes are considered direct. Comparisons of an intervention to placebo or usual care is considered indirect; graded as direct or indirect.
- Precision: describes the level of certainty of the estimate of effect for a particular outcome with a precise estimate being one that allows a clinically useful conclusion; graded as precise or imprecise. When quantitative synthesis is not possible, sample size and assessment of variance within individual studies will be considered.
- Reporting bias: occurs when publication or reporting of findings is based on their direction or magnitude of effect. Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. Reporting bias is difficult to assess as systematic identification of

unpublished evidence is challenging. If sufficient numbers of RCTs (>10) are available, quantitative funnel plot analysis may be done. As a qualitative assessment, clinical trial registries will be searched for unpublished studies and information received in response to the Federal Register notification will be evaluated; graded as suspected or undetected for evidence that is deemed high, moderate, or low.

Bodies of evidence consisting of RCTs are initially considered as high strength while bodies of comparative observational studies begin as low-strength evidence. The strength of the evidence may be downgraded based on the limitations described above. There are also situations where the observational evidence may be upgraded (e.g., large magnitude of effect, presence of dose-response relationship or existence of plausible unmeasured confounders) as described in the AHRQ Methods guides.^{16,19}

A final strength of evidence grade will be assigned by evaluating and weighing the combined results of the above domains. To ensure consistency and validity of the evaluation, the grades will be reviewed by the entire team of investigators. The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale:

- 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.

Summary tables will include ratings for individual strength of evidence domains (risk of bias, consistency, precision, directness) based on the totality of underlying evidence (i.e., the 2018 systematic review⁴ in combination with newly identified studies). We will summarize updated evidence and describe what it adds to the previous review and highlight changes to the key findings.

G. Assessing Applicability

Applicability will be assessed in accordance with the AHRQ's Methods Guide.¹⁶ 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., frequency, administration protocols, duration of therapy and adherence), co-interventions (e.g. medications or other nonpharmacologic interventions), comparisons (e.g., type comparator), 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., timing of intervention and follow-up) 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, particularly primary care, summarizing applicability assessments qualitatively.

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VI. Definition of Terms

None

VII. Summary of Protocol Amendments

None

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions for the original, 2018 review on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized the Key Questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP) as described in the original protocol and final report. This input was intended to ensure that the key questions are specific and relevant. The Key Questions for this update review will not be posted for public comment.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicited input from Key Informants when developing questions for the 2018 systematic review. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. 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 \$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 AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

A TEP for this update review was convened. TEP input was sought to hone and re-affirm methods in the draft protocol, including perspectives on proposed KQ and PICOTS changes, approaches to new data integration, managing challenges and reporting to enhance usability and inform meaningful presentation of the report.

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. 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).

Appendix A. Search strategies: Noninvasive nonpharmacologic treatment of chronic pain.

The following data bases were searched from inception through December, 2016 for the original report. The search was updated November 1, 2017. An updated search for studies published subsequent to our 2018 report was conducted and includes citations from September 1, 2017 through December 11, 2018.

Database: Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2016

- 1 exp Low Back Pain/
- 2 exp Chronic Pain/
- 3 2 and (back or spine or spinal or radicular).ti,ab.
- 4 or/1-3
- 5 Neck Pain/
- 6 exp Osteoarthritis/
- 7 Headache/
- 8 Chronic Pain/
- 9 chronic.ti,ab.
- 10 8 or 9
- 11 10 and (neck or osteoarthritis or fibromyalgia or headache).ti,ab.

- 12 5 or 6 or 7 or 11
- 13 exp Exercise Therapy/

- 14 exp Physical Therapy Modalities/
- 15 exp Braces/

- 16 exp Mind-Body Therapies/
- 17 exp Acupuncture Therapy/
- 18 exp Rehabilitation/
- 19 (4 or 12) and rh.fs.
- 20 19 and multidisciplin\$.mp.
- 21 18 or 20
- 22 exp Psychotherapy/
- 23 exp Musculoskeletal Manipulations/
- 24 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab.
- 25 or/13-17,21-24
- 26 4 and 25
- 27 limit 26 to (english language and humans)
- 28 limit 27 to (meta analysis or randomized controlled trial or systematic reviews)
- 29 27 and (random* or systematic or meta*).ti,ab.
- 30 28 or 29
- 31 limit 30 to yr="2016 -Current"
- 32 12 and 25
- 33 limit 32 to (english language and humans)
- 34 limit 33 to (meta analysis or randomized controlled trial or systematic reviews)

- 35 33 and (random* or systematic or meta*).ti,ab.
- 36 34 or 35
- 37 31 or 36

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

- 1 exp Low Back Pain/
- 2 exp Chronic Pain/
- 3 2 and (back or spine or spinal or radicular).ti,ab.
- 4 or/1-3
- 5 Neck Pain/
- 6 exp Osteoarthritis/
- 7 Headache/
- 8 Chronic Pain/
- 9 chronic.ti,ab.
- 10 8 or 9
- 11 10 and (neck or osteoarthritis or fibromyalgia or headache).ti,ab.
- 12 5 or 6 or 7 or 11
- 13 exp Exercise Therapy/
- 14 exp Physical Therapy Modalities/
- 15 exp Braces/
- 16 exp Mind-Body Therapies/
- 17 exp Acupuncture Therapy/
- 18 exp Rehabilitation/
- 19 (4 or 12) and rh.fs. \
- 20 19 and multidisciplin\$.mp.
- 21 18 or 20
- 22 exp Psychotherapy/
- 23 exp Musculoskeletal Manipulations/
- 24 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab.
- 25 or/13-17,21-24
- 26 4 and 25
- 27 12 and 25
- 28 limit 26 to yr="2016 -Current"
- 29 limit 27 to yr="1996 -Current"
- 30 28 or 29

Database: EBM Reviews - Cochrane Database of Systematic Reviews

- 1 chronic.ti,ab.
- 2 (back or spine or spinal or radicular or neck or osteoarthritis or fibromyalgia or headache).ti,ab.
- 3 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab.
- 4 (exercise or psychosocial or "cognitive behavioral therapy" or CBT or biofeedback or relaxation or "physical modal*" or traction or ultrasound or "transcutaneous electrical nerve stimulation" or TENS or laser or heat or cold or cryotherapy or magnet* or manual* or manipulation or massage or mindfulness or meditation or "mind-body" or

"yoga to tai chi" or qigong or acupuncture or "functional restoration" or "occupational therapy" or multidisciplinary).ti,ab.

5 1 and 2

6 3 or 4

7 5 and 6