Evidence-based Practice Center Systematic Review Protocol

Project Title: Noninvasive, Nonpharmacological Treatment for Chronic Pain

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(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Nature and Burden of Chronic Pain

Chronic pain, defined as pain lasting 12 weeks or longer or persisting past the normal time for tissue healing,[1,2] 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.[2] 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.[3,4] 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.[2] 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,[2] 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.[2] While there are many different underlying causes for chronic pain, this comparative effectiveness review focuses on five common chronic pain conditions: low back pain, neck pain, osteoarthritis, fibromyalgia, and headache. Although many of the same treatments may be employed for each of these conditions, treatment effectiveness may vary across them.

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 nonpharmacological treatments is available for management of chronic pain. An overview of these interventions is briefly presented below.

Pharmacological Treatment

Pharmacological treatments for chronic pain include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, muscle relaxants, antiseizure medications, antidepressants, and corticosteroids. These may be used alone or in combination. 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, but evidence shows only modest short-term benefits.[6-8] Lack of evidence on long-term effectiveness[9] and serious safety concerns[10] speak to the need to consider alternative treatments to opioids. The 2016 *CDC Guidelines for Prescribing Opioids for Chronic Pain* recommend that non-opioid therapy is preferred for the treatment of chronic pain.[11]

Noninvasive, Nonpharmacological Treatment

Noninvasive methods considered for this report will include exercise and physical therapy, mind-body practices (Yoga, Tai Chi, Qigong), psychological therapies (cognitive-behavioral therapy, biofeedback, relaxation techniques, acceptance, and commitment therapy), interdisciplinary rehabilitation, mindfulness practices (meditation, mindfulness-based stress reduction practices), osteopathic and spinal 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), acupuncture, and functional restoration training. Across many chronic pain conditions, exercise is commonly recommended.

One primary challenge for this review is its breadth; it encompasses five diverse conditions for which over a dozen different interventions will be considered. Across the conditions and interventions, the literature base is large and complex, which poses another challenge to this review. These challenges speak to the need for focusing the review in order to provide meaningful and useful evidence synthesis. Other challenges related to the evidence and its synthesis include: (1) the most appropriate outcomes to assess, their diversity, and the need to consider multiple outcomes related to pain, function, and quality of life, (2) understanding the clinical meaningfulness of observed effects, (3) heterogeneity within the conditions and generalizability of evidence across subpopulations, (4) optimal methods for administering noninvasive therapies (e.g., the

number, duration, or intensity of treatment sessions and adherence), and (5) difficulty in effectively blinding for some nonpharmacological therapies.

Rationale for Evidence Review

The burden of chronic pain, numerous treatment options available, and lack of recent comprehensive evidence reviews on nonpharmacological treatment options for the different chronic pain conditions included in this review warrant a comprehensive evidence synthesis to guide clinical and policy decisionmaking.

Of the five conditions, two (low back pain and osteoarthritis) have been the subject of recent reviews published by the Agency for Healthcare Research and Quality (AHRQ). The low back pain comparative effectiveness review focused on the comparative benefits and harms of noninvasive treatments and provided a comprehensive evaluation of noninvasive, nonpharmacological low back pain treatments from the literature through August 2014,[12] with an updated search for literature through February 2016 for related recent publications.[13,14] Additional potentially relevant studies have been published.

A recently available AHRQ draft report on treatment of primary and secondary osteoarthritis[15] may provide some evidence from literature through late 2016 on physical therapy, exercise, certain physical modalities, and manual therapy, but does not address interventions such as Yoga, Tai Chi, acupuncture, or psychological therapies that are relevant to our review.

The other three conditions (chronic neck pain, fibromyalgia, and headache) have been the subject of numerous systematic reviews; however, these reviews do not appear to address the breadth of interventions considered for this review. In addition, it appears that there is substantial overlap across systematic reviews regarding included randomized controlled trials (RCTs) for specific interventions and conditions.

What this Review Adds

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.[2,5] 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),[11] 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 nonpharmacological treatment. These initiatives, and others, speak to the importance of understanding current evidence on

noninvasive, nonpharmacological treatment of chronic pain. Given this need and wide-spread concern regarding opioid use and misuse outlined in recent guidelines and reviews, the impact of this report is potentially far-reaching. The evidence synthesized in this review may help inform guidelines and health care policy (including reimbursement policy) related to use of noninvasive, nonpharmacological, and pharmacological treatments as alternatives to opioids and some pharmacological treatments for management of common chronic pain conditions. The report will help address some of the needs described in the NPS[5] and IOM[2] reports and others for evidence regarding treatment options. This review may also provide additional insights into research gaps related to use of noninvasive, nonpharmacological alternatives for treating chronic pain.

II. The Key Questions

Provisional Key Questions, patients, interventions, comparators, outcomes, timing, settings, and study design (PICOTS), and analytic framework for this topic were posted on the AHRQ Website from December 27, 2016 to January 23, 2017. Most comments noted that there was substantial heterogeneity within the included chronic pain conditions and within categories of nonpharmacological, noninvasive treatment strategies. Suggestions for including additional chronic pain conditions and additional interventions were made; however all were considered beyond the scope and resources for this review. Similarly, suggestions for including additional Key Questions were considered to be out of the scope of this review.

In response to questions regarding types of comparators to be used, information about the research concepts addressed by the choice of comparators for the subquestions is now listed after the Key Questions.

Refinement of the PICOTS table based on public comment included the following:

- Clarification that focus for Key Question 1 is on nonradicular low back pain; exclusion of failed back surgery syndrome
- Clarification that exercise that is part of physical therapy is included for exercise (not equating exercise with physical therapy)
- Clarification that formal exercise programs, including both those that are directly supervised and those that are home-based based are to be included; general physical activity that is not part of a formal exercise program is not included
- Clarification of intermediate term to be 6-12 months.
- Clarification that cross-over trial designs using random assignment of initial treatment meet conceptual standards for a randomized controlled trial.

The final Key Questions are as follows:

1. In adults with chronic low back pain:
    a. What are the benefits and harms of noninvasive nonpharmacological therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
    b. What are the benefits and harms of noninvasive nonpharmacological therapies compared with pharmacological therapy (e.g., opioids, NSAIDS, acetaminophen, antiseizure medications, antidepressants)?

c. What are the benefits and harms of noninvasive nonpharmacological therapies compared with exercise?

2. In adults with chronic neck pain:
    a. What are the benefits and harms of noninvasive nonpharmacological therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
    b. What are the benefits and harms of noninvasive nonpharmacological therapies compared with pharmacological therapy?
    c. What are the benefits and harms of noninvasive nonpharmacological therapies compared with exercise?
3. In adults with osteoarthritis-related pain:
    a. What are the benefits and harms of noninvasive nonpharmacological therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
    b. What are the benefits and harms of noninvasive nonpharmacological therapies compared with pharmacological therapy?
    c. What are the benefits and harms of noninvasive nonpharmacological therapies compared with exercise?
4. In adults with fibromyalgia:
    a. What are the benefits and harms of noninvasive nonpharmacological therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
    b. What are the benefits and harms of noninvasive nonpharmacological therapies compared with pharmacological therapy?
    c. What are the benefits and harms of noninvasive nonpharmacological therapies compared with exercise?
5. In adults with chronic tension headache:
    a. What are the benefits and harms of noninvasive nonpharmacological therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
    b. What are the benefits and harms of noninvasive nonpharmacological therapies compared with pharmacological therapy?
    c. What are the benefits and harms of noninvasive nonpharmacological therapies compared with biofeedback?
6. Do estimates of benefits and harms differ by age, sex, or presence of comorbidities (e.g., emotional or mood disorders)?

The three-part format for the Key Questions reflects the following research concepts:

- Part "a" answers the question of whether the various interventions work overall compared with sham, waitlist control, attention control, no treatment or usual care.
- Part "b" answers the question of whether the various interventions work compared with pharmacological alternatives.

- Part "c" answers the question of how outcomes for individual interventions (e.g., acupuncture) compare with a common comparator. Exercise is the most frequent comparison in the literature for many chronic pain conditions, so it provides a common comparator for analysis. It is also recommended in most guidelines for conditions including low back pain, neck pain, fibromyalgia, and osteoarthritis and is widely available. Exercise will serve as common comparator for these conditions. For chronic headache, biofeedback will provide a common comparator for analysis.

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

- Population(s): 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 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
  - Functional restoration training
  - Multidisciplinary/interdisciplinary rehabilitation.
- Comparators:
  - **For all Key Questions, subquestion "a"**
    - Sham treatment
    - Waitlist
    - Usual care
    - Attention control
    - No treatment
  - **For all Key Questions, subquestion "b"**
    - Non-opioid pharmacological therapy(nonsteroidal anti-inflammatory drugs, acetaminophen, antiseizure medications, antidepressants)
    - 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.

The focus for this review is on understanding the effectiveness of individual nonpharmacological interventions that may be alternatives to opioid use, particularly over the long-term base on primary literature. The intended focus is on single active interventions and comparators. To facilitate this, major decisions and related rationale include:

- Exclusion of studies evaluating the incremental value of adding a noninvasive, nonpharmacological intervention (or component of such an intervention) to another noninvasive, nonpharmacological intervention. Given the numerous potential combinations of therapies (and few studies for any given comparison), it would be difficult to draw evidence-based conclusions across studies regarding individual, specific, noninvasive, nonpharmacological treatments.
- Exclusion of comparisons within nonpharmacological intervention types (e.g., comparisons of different types of exercise with each other, different types of massage with each other). Comparison of the different nonpharmacological, noninvasive treatments to a common nonpharmacological comparator (e.g., exercise) was considered to be of more value for initial evaluation of effectiveness and to maintain a manageable scope for this review.
- Exclusion of studies that compare noninvasive, nonpharmacological intervention to each other. To include such comparisons would expand the scope and add to the complexity of the report. The evidence base is likely not very strong as there are likely too few studies for each comparison and numerous methodological issues would likely preclude drawing evidence-based conclusions.
- Self-management and self-management education programs were considered, however their inclusion would expand the scope of this project beyond available

resources; they will be excluded.

- Three general categories of comparator will be employed:
    - To evaluate the question whether the various interventions work overall, they will be compared with sham, waitlist control, attention control, no treatment, or usual care for subquestion "a". These control types are frequently used comparators for a variety of interventions and provide valuable information regarding the efficacy of a treatment for pain by controlling for nonspecific factors that may impact outcomes. Subjective improvement in patients may result from factors other than a given procedure, whether that treatment is an "active" sham or a specified intervention. Some of these factors include the natural course of the condition, the effects of placebo, and measurement error. A placebo effect does not require a placebo and reflects a change in a patient's condition attributable to the symbolic importance of a treatment versus specific physiologic or pharmacologic properties of a treatment.[16,17] We recognize that definitions and components of these types of controls are not standardized and likely vary across studies. We will abstract definitions and details regarding the provision and components of the control treatments and where commonality exists, consider grouping similar types together and heterogeneity may be discussed as a limitation of the evidence.
    - Interventions will be compared with pharmacological alternatives which are commonly used for management of chronic pain for subquestion b. We recognize that pharmacological treatment may likely be concomitant with interventions. We will abstract details of the pharmacological treatments.
    - Evaluation of how outcomes for individual interventions (e.g., acupuncture) compare with a common comparator for subquestion "c", allows us to focus the scope of the report while providing a potentially meaningful comparison across interventions. Exercise has been chosen as the common comparator for Key Questions 1-4 (i.e., for low back pain, chronic neck pain, osteoarthritis, fibromyalgia) given that it is readily accessible, is the most frequent comparison in the literature for many chronic pain conditions, and is recommended in most guidelines for these conditions. Biofeedback will serve as the common comparator for chronic tension-type headache as it is a well-accepted intervention that has been studied for tension-type headaches.
- Exclusion of studies that do not have at least 4 weeks followup post intervention. While immediate/short-term improvement is of value, given that the conditions are chronic, evaluation of longer-term impact and sustainability of effects is considered to be more important.

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

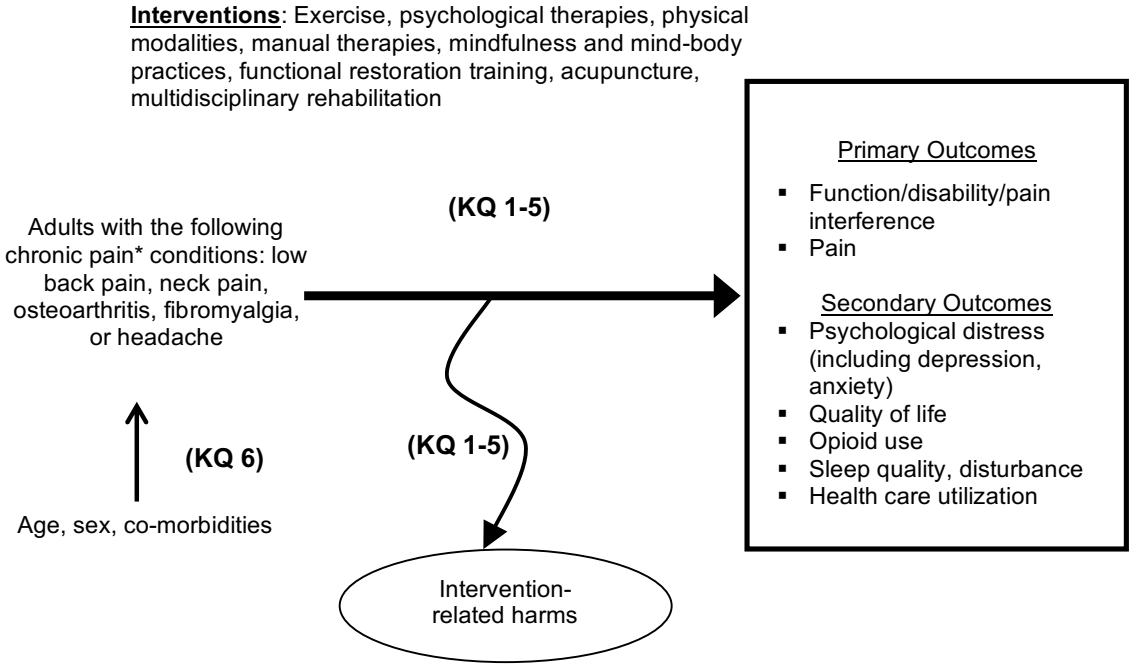
- Regarding conditions, we will abstract details for each condition including diagnostic criteria used and stratify as possible (e.g., by etiology of low back pain or affected area for osteoarthritis such as hip or knee). It is likely that trials vary in

regard to the degree to which characteristics of the condition 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.

III. Analytic Framework

Figure 1. Analytic framework for noninvasive, nonpharmacological treatment for chronic pain



KQ=Key Question
*Chronic 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

	Inclusion	Exclusion

Patients	**General Inclusion Criteria**
	• 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, tension or mixed headache.
	
	KQ1: Low back pain
	Adults with chronic, nonradicular low back pain
	
	KQ2: Neck pain
	• Adults with chronic neck pain
	
	KQ3: Osteoarthritis
	• Adults with osteoarthritis-related pain (primary or secondary osteoarthritis) of the hip, knee or hand
	
	KQ4: Fibromyalgia
	• Adults with fibromyalgia
	
	KQ5: Headache
	• Adults with primary chronic tension headache.
	  ○ 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.
		General Exclusion Criteria
		• Acute pain
		• Children (<18 years), pregnant or breastfeeding women
		• 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
		
		KQ1: Low back pain
		• Patients with radiculopathy
		• Low back pain associated with severe or progressive neurological deficits
		• Failed back surgery syndrome
		
		KQ2: Neck pain
		• Patients with radiculopathy or myelopathy
		• Traumatic spinal cord injury
		• Neck pain associated with progressive neurological deficit, loss of strength
		
		KQ3: Osteoarthritis
		• Other types of arthritis (e.g., rheumatoid)
		• Patients with joint replacement
		
		KQ4: Fibromyalgia
		• Conditions with generalized pain not consistent with fibromyalgia
		  • Systemic exertion intolerance disease, (myalgic encephalomyelitis/chronic fatigue syndrome)
		• Somatization disorder (Briquet's syndrome)
		
		KQ5: Headache
		• Migraine headache
		• Mixed headache (also known as co-existent tension and migraine headache, chronic daily headache, transformed migraine)
		• Trigeminal neuralgia
		• Cluster headache
		• Secondary headache types as defined in *The International Classification of Headache Disorders*, 3rd edition (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

	Inclusion	Exclusion
Interventions	**All KQs:** • 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 [TENS], low level laser therapy, interferential therapy, electro-muscular stimulation [EMS] diathermy, superficial heat or cold, bracing for knee, back, neck, hand and magnets) • Manual therapies (manipulation, massage) • Mindfulness practices (meditation, mindfulness-based stress reduction practices) • Mind-body practices (Yoga, Tai Chi, Qigong) • Acupuncture • Functional restoration training • Multidisciplinary/interdisciplinary rehabilitation*	**All KQs:** • 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, nonpharmacological intervention to another noninvasive, nonpharmacological intervention • Self-management interventions or programs, self-management education programs • Others not listed for inclusion
Comparators	**All KQs, subquestion a** • Sham treatment • Waitlist • Usual care • No treatment • Attention control intended to control for nonspecific effects (e.g., time, attention, expectations); **All KQs subquestion b** • Non-opioid pharmacological therapy (NSAIDS, acetaminophen, anti-seizure medications, antidepressants) • Opioid analgesics **KQs 1-4, 6 subquestion c** • Exercise† **KQ 5, 6 subquestion c** • Biofeedback‡	**All KQs:** • Supplements (e.g. glucosamine, chondroitin, d-ribose, herbal or homeopathic treatments) • Over-the-counter topical agents (e.g., aloe, capsaicin) • Invasive nonsurgical treatments (e.g., injections, nerve block, spinal cord stimulators, parenterally-administered medications) • Surgical interventions (including minimally invasive surgical interventions) • Studies evaluating incremental value of adding a noninvasive, nonpharmacological intervention to another noninvasive, nonpharmacological intervention • Comparisons within nonpharmacological intervention types (e.g., comparisons of different types of exercise with each other, different types of massage with each other) • Others not listed for inclusion

	Inclusion	Exclusion
Outcomes	**All KQs:** Primary efficacy outcomes; we will focus on outcomes from validated measures for • Function/disability/pain interference[§] • Pain[§] Harms and Adverse effects Secondary outcomes • Psychological distress (including measures of depression and anxiety) • Quality of life • Opioid use • Sleep quality, sleep disturbance • Health care utilization	**All KQs:** • 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.	**All KQs:** • 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 **KQ 1:** • For chronic low back pain, studies published prior to February 2016 will be considered to have been incorporated in the previous review on low back pain and will be excluded here. **KQ 2, 3, 4, 5, 6:** • 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).
Setting(s)	Any nonhospital setting or in self-directed care	• Hospital care, hospice care, emergency department care

	Inclusion	Exclusion
Timing	Duration of followup: short term (up to 6 months), intermediate term (6-12 months) and long term (at least 1 year); focus on longer term (>1 year) effects. Trials lasting ≥ 6 months which 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.	• Studies with <1 month followup after treatment

NSAID: nonsteroidal anti-inflammatory drug
*Multidisciplinary rehabilitation (also known as interdisciplinary rehabilitation, is defined as a coordinated program with both physical and biopsychosocial treatment components (e.g., exercise therapy and cognitive behavioral therapy) provided by professionals from at least two different specialties.
†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.
‡Different forms of biofeedback will not be compared to each other. Biofeedback will be compared with the noninvasive interventions for chronic headache.
§The magnitude of effects for pain and function will be classified using the same system as in the AHRQ-funded noninvasive treatment for low back pain review 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 analogue scale (VAS), 0.5 to 1.0 points on a 0- to 10-point numerical 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 condition. 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.

Below are additional details on the scope of this project:

Study Designs: The focus of this review is on RCTs reporting on longer-term outcomes (at least 4 weeks post intervention) that otherwise meet our PICOTS criteria. If more than 10 RCTs for a given comparison are identified, systematic reviews of randomized trials that report data for longer term outcomes may be considered if they address a Key Question, include studies that meet the PICOTS as defined above, and are assessed as being at low risk of bias, according to the ROBIS quality assessment tool.[18,19] Data on outcomes and timeframes of interest for our review will be abstracted. If the previous review includes some but not all relevant outcomes, we will consult the primary studies and abstract additional data as needed. Data from studies used in previous systematic reviews will be combined with data from other, 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. If multiple systematic reviews are identified, we will focus on the one or two most recent, relevant reviews of highest quality. 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.

For chronic low back pain, we will focus on RCTs and reviews published subsequent to the February 2016 search date from the recent review update for journal publication; this will enhance analytic efficiency for this condition given the large body of evidence that has already been synthesized. RCTs will be considered and those included will be critically appraised. 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 without restriction on publication date for all conditions with the exception of low back pain. For chronic low back pain, for interventions addressed in the prior AHRQ low back pain review, we will identify trials published prior to February 2016 from the AHRQ report and updates. Magnets were not covered in the prior review. For the current review we will search for evidence on magnets without restriction on publication date.

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

Literature Databases: Ovid MEDLINE, 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.

Federal Register Notice (in lieu of Scientific Information Packets [SIPs]): 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.

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*.[18] 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 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 templates, data from included 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), intervention characteristics (including the type, number, intensity, duration of, and adherence to treatments), comparator characteristics, and results including harms. Input from the Key Informants and Technical Expert Panel on clinically important outcomes for each condition was combined with team expertise to prioritize function, pain, quality-of-life outcomes, and harms for synthesis. 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.

For systematic reviews we will abstract the following data: inclusion criteria, search strategy, databases searched, search dates, the number of included studies, study characteristics of included studies (e.g., sample sizes, interventions, comparison, and results), methods of quality assessment, quality ratings for included studies, methods for synthesis, and results.

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

D. Assessment of Methodological Risk of Bias of Individual Studies

Predefined criteria 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)*,[20] and precepts for appraisal developed by the Cochrane Back and Neck Group.[21] Systematic reviews will be assessed using the ROBIS tool for assessing risk of bias in systematic reviews.[19] 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,[22] from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[18] 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.

For systematic reviews, we will only include studies rated "good," or "low risk of bias" based on use of multiple sources in the literature search, application of pre-defined inclusion and exclusion criteria, assessment of risk of bias for individual studies using an appropriate tool, use of methods to reduce errors in data abstraction and quality rating (e.g., multiple independent reviewers), appropriate methods for evidence synthesis (qualitative or quantitative), and an explicit system for considering the body of evidence that includes the major domains of strength of evidence (risk of bias, consistency, precision, and directness).

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 construct 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. Evidence tables will also include relevant studies from the prior low back pain review as appropriate, as well as new studies identified in current searches. We will summarize findings from prior systematic reviews assessed as being at low risk of bias (i.e., good quality), including the number and types of studies included and overall findings, separately from newly identified studies. Evidence from both the prior review and any new studies will then be synthesized jointly and we will assess strength of evidence and draw conclusions based on the totality of evidence available.

Findings will be synthesized qualitatively (based on ranges and descriptive analysis, with interpretation of results) and quantitatively (meta-analysis) when appropriate. To the extent that the interventions are distinct, we will separate them out for analysis and reporting; interventions with similar characteristics may be combined. For example, similar types of exercise with similar delivery and duration, such as aerobic exercise, may be combined together but would not be combined with resistance training. Meta-analyses will be conducted to summarize data and obtain more precise estimates on primary outcomes 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.[18] In general, pooling would be considered if at least five trials are available for a specific comparison and primary outcome. The number of studies, chosen *a priori,* may facilitate examination of clinically or methodologically important study characteristics and helps avoid concerns related to statistical under-estimation of heterogeneity and uncertainty that may be related to meta-analysis of a small number of studies.[23] 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.[23-25] If there are >10 RCTs for a given comparison, previously published meta-analyses that meet our criteria may be used. If new studies not included in the meta-analysis are identified, decisions regarding whether to perform an updated meta-analysis will be based on the precision of the pooled estimate, the consistency of results from new studies compared to the pooled estimate, and the likelihood that results from new studies would impact conclusions and estimates. To the extent that the interventions within a given category are distinct we will separate them out for analysis and reporting. 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.[26]

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., hand, knee, hip).

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.[18] The initial assessment will be independently reviewed by at least one other experienced investigator. Initial prioritization of primary comes reflected in the PICOTS table is based on input from the Key Informants in combination with team expertise. The listed outcomes were considered to be most clinically relevant and important to patients. We have incorporated input from the Technical Expert Panel on clinically important outcomes for each condition to further prioritize functional, pain, quality-of-life 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 on 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.[18,22]

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., in previously published systematic reviews and in newly identified studies).

G. Assessing Applicability

Applicability will be assessed by examining the characteristics of the patient populations for each condition (e.g., demographic characteristics, condition-

specific diagnostic criteria, symptoms, presence of medical and psychiatric co-morbidities, other psychosocial factors); the interventions (e.g., availability in the United States; dose, frequency, or intensity of treatment, and methods for administration); and clinical settings (e.g., primary care, specialty setting; developing country versus developed country) in which the included studies are performed. Issues with applicability may limit the ability to generalize the results to other populations and settings.

V. References

1. [No authors listed]. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Suppl. 1986;3:S1-226. PMID: 3461421.
2. Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011.
3. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. Clin J Pain. 2008 Jul-Aug;24(6):469-78. doi: 10.1097/AJP.0b013e31816b2f26. PMID: 18574357.
4. Eriksen J, Sjogren P, Bruera E, et al. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain. 2006 Nov;125(1-2):172-9. doi: 10.1016/j.pain.2006.06.009. PMID: 16842922.
5. National Pain Strategy Task Force. National Pain Strategy: A Comprehensive Population Health-Level Strategy for Pain. Interagency Pain Research Coordinating Committee (IPRCC), National Institutes of Health (NIH); 1-83. 2015. https://iprcc.nih.gov/National_Pain_Strategy/NPS_Main.htm.
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 Dec;18(12):1166-75. doi: 10.1002/pds.1833. PMID: 19718704.
7. 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.
8. Sullivan MD, Edlund MJ, Fan MY, 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 Aug 31;138(2):440-9. doi: 10.1016/j.pain.2008.04.027. PMID: 18547726.
9. 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 Feb 17;162(4):276-86. doi: 10.7326/M14-2559. PMID: 25581257.
10. 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.
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. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatment for Low Back Pain. Comparative Effectiveness Review No. 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. HHSA 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Rockville, MD: Agency for Healthcare Research and

Quality. February 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm. PMID: 26985522.
13. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2017 Feb 14;166:[Epub ahead of print]. doi: 10.7326/M16-2459. PMID: 28192793.
14. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2017 Feb 14;166:[Epub ahead of print]. doi: 10.7326/M16-2458. PMID: 28192790.
15. Draft Comparative Effectiveness Review. Treatment of Primary and Secondary Osteoarthritis of the Knee: An Update Review [in progress]. Prepared for Agency for Healthcare Research and Quality. Rockville, MD: Forthcoming.
16. Meissner K, Fassler M, Rucker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA Intern Med. 2013 Nov 25;173(21):1941-51. doi: 10.1001/jamainternmed.2013.10391. PMID: 24126676.
17. Turner JA, Deyo RA, Loeser JD, et al. The importance of placebo effects in pain treatment and research. JAMA. 1994 May 25;271(20):1609-14. PMID: 7880221.
18. . Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
19. Whiting P, Savovic J, Higgins JP, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016 Jan;69:225-34. doi: 10.1016/j.jclinepi.2015.06.005. PMID: 26092286.
20. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from http://handbook.cochrane.org.; 2011.
21. 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.
22. Viswanathan M, Ansari MT, Berkman ND, et al. Chapter 9: Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
23. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014 Feb 18;160(4):267-70. doi: 10.7326/M13-2886. PMID: 24727843.
24. Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. Stat Med. 1996 Mar 30;15(6):619-29. doi: 10.1002/(SICI)1097-0258(19960330)15:6<619::AID-SIM188>3.0.CO;2-A. PMID: 8731004.
25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 06;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120.
26. 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.

VI. Definition of Terms

None

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
September 20, 2017	IV. Methods, E. Data Synthesis	In general, pooling would be considered if at least five trials are available for a specific comparison and primary outcome.	In general, pooling would be considered if at least two trials are available for a specific comparison and primary outcome.	To facilitate comparisons across interventions.

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions 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). This input is intended to ensure that the key questions are specific and relevant.

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 solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. 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.

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, nonpharmacological treatment of chronic pain.

The following data bases were searched from inception through December, 2016

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 November 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 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 2005 to December 21, 2016

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