

## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Noninvasive Treatments for Low Back Pain

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

**Nature and burden of low back pain.** Low back pain is one of the most frequently encountered conditions in clinical practice. Up to 84 percent of adults have low back pain at some time in their lives, and over one quarter of U.S. adults report recent (in the last three months) low back pain.<sup>1,2</sup> Low back pain can have major adverse impacts on quality of life and function; it is frequently associated with depression or anxiety. Low back pain is also costly—in 1998, total U.S. health care expenditures for low back pain were estimated at \$90 billion.<sup>3</sup> Since that time, costs of low back pain care have risen at a rate higher than observed for overall health expenditures.<sup>4</sup> Low back pain is one of the most common reasons for missed work or reduced productivity while at work, resulting in high indirect costs.<sup>5</sup>

The prognosis for acute low back pain (generally defined as an episode lasting less than 4 weeks) is generally favorable. Most patients experience a rapid improvement in (and often a complete resolution of) pain and disability and are able to return to work.<sup>6</sup> In those with persistent symptoms, continued improvement is often seen in the subacute phase between 4–12 weeks, though at a slower rate than observed at first. In a minority of patients, low back pain lasts longer than 12 weeks, at which point it is considered chronic; levels of pain and disability often remain relatively constant thereafter.<sup>7</sup> Recently, a National Institutes of Health Research Task Force defined chronic low back pain as a back pain problem that has persisted at least 3 months and has resulted in pain on at least half the days in the past 6 months.<sup>8</sup> Patients with chronic back pain account for the bulk of the burdens and costs of low back pain.<sup>9,10</sup> Predictors of chronicity are primarily related to psychosocial factors such as presence of psychological comorbidities, maladaptive coping strategies (such as fear avoidance [avoiding activities because of fears that they will further damage the back] or catastrophizing [anticipating the worst possible outcomes from low back pain]), presence of nonorganic signs (symptoms without a distinct anatomical or physiological basis),<sup>11</sup> high baseline functional impairment, low general health status, and others.<sup>7</sup>

In the majority (>85%) of patients with low back pain, symptoms cannot be attributed to a specific disease or spinal pathology.<sup>12</sup> Spinal imaging abnormalities such as degenerative disc disease, facet joint arthropathy, and bulging or herniated intervertebral discs are extremely common in patients with low back pain, particularly in older adults, and such findings are poor predictors for the presence or severity of low back pain.<sup>13</sup> Radiculopathy from nerve root impingement (often due to a herniated intervertebral disc) and radiculopathy from spinal stenosis (narrowing of the spinal canal) are each present in about 4–5 percent of patients with low back pain and can cause neurological symptoms such as lower extremity pain, paresthesias, and weakness; the natural history and response to treatment for these conditions may differ from back pain without neurologic involvement.<sup>14</sup>

**Interventions for low back pain.** Multiple treatment options for acute and chronic low back pain are available. Broadly, these can be classified as pharmacological treatments,<sup>15</sup> noninvasive nonpharmacological treatments,<sup>16</sup> injection therapies,<sup>17</sup> and surgical treatments.<sup>18</sup> The report focuses on the comparative benefits and harms of pharmacological and noninvasive nonpharmacological treatments; each of these categories encompass a number of different therapies. Pharmacological treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, muscle relaxants, antiseizure medications, antidepressants, and corticosteroids; nonpharmacological treatments include exercise and related interventions (e.g., yoga), complementary and alternative therapies (e.g., spinal manipulation, acupuncture, and massage), psychological therapies (e.g., cognitive-behavioral therapy, relaxation techniques, and interdisciplinary rehabilitation), and physical modalities (e.g., traction, ultrasound, transcutaneous electrical nerve stimulation [TENS], low level laser therapy, interferential therapy, superficial heat or cold, back supports, and magnets). Important challenges in conducting a review of this topic include the large number of treatment options, potential variability in response to treatment depending on patient characteristics, difficulty in effectively blinding many of the nonpharmacological therapies (e.g., exercise or psychological therapies), the need to consider multiple outcomes related to both pain and function, and the relative paucity of evidence for specific low back conditions such as radiculopathy and spinal stenosis.

**Rationale for evidence review.** The burden of low back pain, the numerous non-invasive treatment options to be considered by clinicians and patients, and the availability of new evidence and interventions (e.g., duloxetine) warrant a comprehensive comparative effectiveness review of this topic. An existing guideline<sup>14</sup> and associated systematic reviews<sup>15,16</sup> from the American College of Physicians and the American Pain Society were published in 2007, emphasizing the role of pharmacological therapies and non-invasive non-pharmacological therapies for low back pain in most situations. A systematic evidence review that included recently published research may provide a better understanding of the comparative effectiveness of treatment options for acute and chronic low back pain and could be used to update existing clinical recommendations that could be out of date. To aid in the efficiency of the review process, this review will be conducted as an update of prior systematic reviews on pharmacological and non-pharmacological, non-invasive treatments used to develop the 2007 ACP/APS clinical practice guideline and conducted by the same review team.<sup>15,16</sup>

## II. The Key Questions

The provisional Key Questions, PICOTS, and analytic framework for this topic were posted on the AHRQ Web site for public comment from December 17, 2013, through January 17, 2014. We made changes in response to public comments, as follows. The PICOTS were revised to include Tai Chi as an intervention and time between back pain episodes as an outcome, and the Key Questions and PICOTS were revised to include combinations of therapies as interventions and comparators. We made additional wording edits to the Key Questions to clarify inclusion of oral and topical pharmacological therapies and to group the nonpharmacological, noninvasive therapies into related categories (exercise and related interventions, complementary and alternative therapies, psychological therapies, and physical modalities). We revised the PICOTS to be clearer that the population included patients with acute, subacute, or chronic low back pain, and added self-directed care to the setting description.

**Key Question 1 (KQ1)**

What are the comparative benefits and harms of different oral or topical pharmacological therapies or combinations thereof (combinations may include both pharmacological and nonpharmacological components) for acute, subacute, or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis?

**Key Question 2 (KQ2)**

What are the comparative benefits and harms of different nonpharmacological, noninvasive therapies, or combinations thereof (combinations may include both pharmacological and nonpharmacological components) for acute, subacute, or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis, including but not limited to exercise and related interventions, complementary and alternative therapies, psychological therapies, physical modalities, and interdisciplinary rehabilitation?

**Key Question 3 (KQ3)**

How do the benefits of pharmacological or nonpharmacological therapies for low back pain vary according to patient characteristics (e.g., demographic, clinical, and psychosocial risk factors)?

**PICOTS****Population(s)**

- Adults with acute (<4 weeks), subacute (4-12 weeks), or chronic (>12 weeks) nonradicular low back pain, radicular low back pain, or symptomatic spinal stenosis.
- Exclude: Children, pregnant women
- Exclude: Patients with low back pain related to cancer, infection, inflammatory arthropathy, high velocity trauma, fracture; or low back pain associated with severe or progressive neurological deficits

**Interventions****KQ1: Oral or topical pharmacologic therapies (or combinations thereof)**

- Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, celecoxib, acetylsalicylic acid (aspirin)
- Nonopioid analgesics, such as acetaminophen
- Opioid analgesics, such as oxycodone, hydrocodone, hydromorphone, morphine, fentanyl
- Tramadol and tapentadol
- Antidepressants, such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin-reuptake inhibitors (SSRIs), or serotonin antagonist and reuptake inhibitors (SARIs)
- Skeletal muscle relaxants
- Benzodiazepines
- Corticosteroids, such as prednisone or prednisolone
- Anti-epileptic drugs, such as gabapentin or pregabalin
- Capsaicin or topical lidocaine
- Exclude: Parenterally administered medications

## KQ2: Noninvasive, nonpharmacological therapies (or combinations thereof)

- Interdisciplinary or multicomponent rehabilitation
- Psychological therapies, such as cognitive behavioral therapy
- Exercise and related interventions, such as yoga or Tai Chi
- Complementary and alternative medicine therapies: spinal manipulation, acupuncture, massage
- Passive physical modalities: heat, cold, ultrasound, transcutaneous electrical nerve stimulation (TENS), electrical muscle stimulation (EMS), interferential therapy (IFT), traction, low level laser therapy, lumbar supports/braces
- Other noninvasive treatments, such as taping
- Exclude: Invasive, nonsurgical therapies (e.g., injections) and surgical therapies

### **Comparisons**

- Any included pharmacological or non-pharmacological intervention or combination of interventions (combinations may include both pharmacological and nonpharmacological components) versus any other included intervention or combination of interventions, placebo (drug trials), sham (functionally-inert) treatments, or no treatment.

### **Outcomes**

- Final health outcomes
  - Reduction or elimination of low back pain, including related leg symptoms
  - Improvement in back-specific and overall function
  - Improvement in health-related quality of life (HRQOL)
  - Reduction in work disability/return to work
  - Global improvement
  - Number of back pain episodes or time between episodes
  - Patient satisfaction
- Adverse effects of intervention(s)
  - *Pharmaceutical*: serious (anaphylaxis, death) and nonserious (mild allergic or untoward) drug reactions or effects; opioid addiction or overdose
  - *Nonpharmaceutical*: serious (death, neurological including cauda equine syndrome, fracture, local skin burns, etc.) and nonserious (mild transient local or general soreness, stiffness, aching; local skin irritation, etc.)

### **Timing**

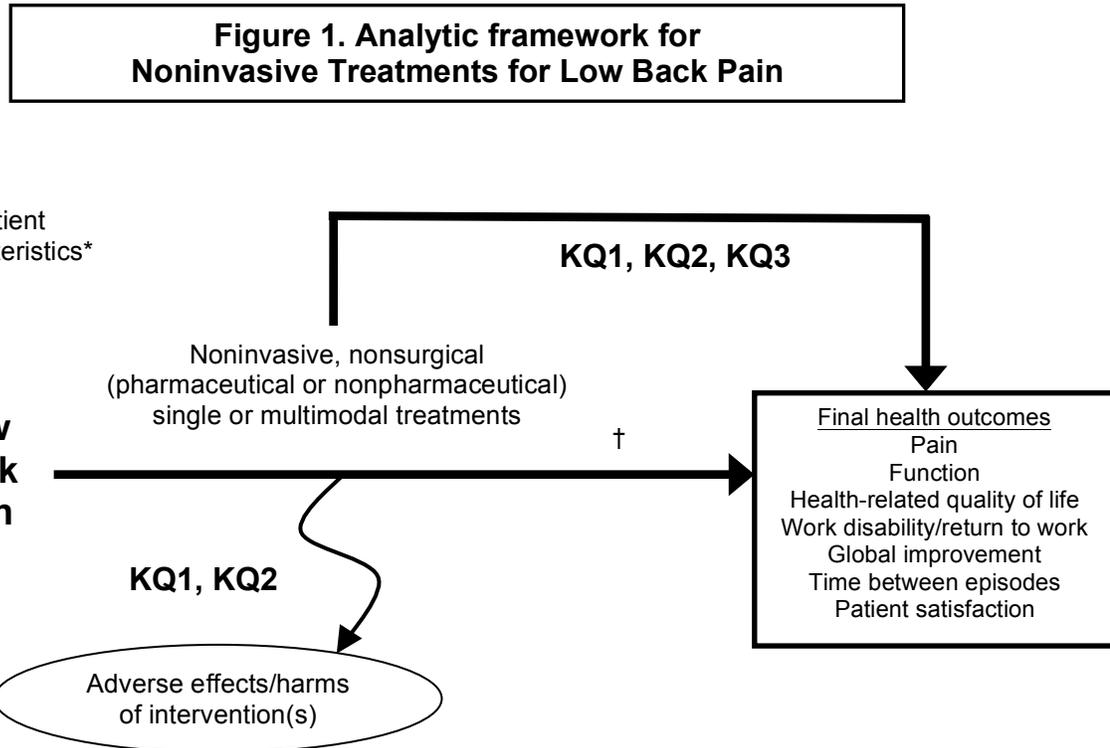
- Duration of followup: short term (up to 6 months) and long term (at least 1 year)

### **Setting**

- Any nonhospital setting or in self-directed care

### III. Analytic Framework

The analytic framework illustrates the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis.



\* Patient characteristics include clinical, demographic, and psychosocial risk factors associated with low back pain outcomes.

† Intermediate outcomes are typically not measured (e.g., inflammation).

## IV. Methods

### A. Criteria for Inclusion/Exclusion of Studies in the Review

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

Below are additional details on the scope of this project:

**Study Designs.** Given the large number of interventions and comparisons addressed in this review, systematic reviews of randomized trials will be used if they address a key question, include studies that meet the PICOTS as defined above, and are assessed as good-quality using the AMSTAR quality assessment tool.<sup>19,20</sup> We will exclude outdated systematic reviews, defined as systematic reviews for which searches ended prior to 2009. If systematic reviews are included, we will update findings with any new primary trials identified in our searches, update meta-analyses if appropriate, and re-assess strength of evidence based on the totality of evidence. If multiple systematic reviews are relevant and good-quality, we will focus on the findings from the most recent reviews, evaluate areas of consistency and inconsistency across the reviews, and assess strength of evidence based on the totality of evidence.<sup>20,21</sup> For harms, we will include cohort studies or interventions and comparisons when randomized trials are sparse or unavailable. We will exclude case-control studies, case reports, and case series.

**Non-English-Language Studies.** We will only include non-English-language articles included in English-language systematic reviews. We will review English-language abstracts of non-English-language articles to identify studies that would otherwise meet inclusion criteria, in order to help assess for the likelihood of 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 begin in January 2006, as systematic evidence reviews conducted for an ACP/APS clinical practice guideline addresses the interventions covered in the current review and conducted searches through November 2006.

Electronic database 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 new pertinent literature is identified for inclusion in the update search process, it will be incorporated prior to final submission of the report.

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

**Scientific Information Packets.** Companies that manufacture non-generic medications for low back pain will be invited to provide Scientific Information Packets.

**Hand Searching.** Reference lists of included articles will 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 based on the PICOTS will be used to determine eligibility for inclusion and exclusion of abstracts in accordance with the AHRQ Methods Guide.<sup>19</sup> All excluded abstracts will be reviewed by at least two reviewers. All citations deemed appropriate for inclusion by at least one of the reviewers will be retrieved. Each full-text article will be independently reviewed for eligibility by two team members, including any articles suggested by peer reviewers or that arise from the public posting process. Any disagreements will be resolved by consensus. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

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

After studies are selected for inclusion, we will abstract the following data for each randomized trial or cohort study: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results. Information relevant for assessing applicability will also be abstracted, including the characteristics of the population, interventions, and care settings; the use of run-in or washout periods, 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 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 individual controlled trials, systematic reviews, and observational studies by using clearly defined templates and criteria as appropriate. Randomized trials will be evaluated with appropriate criteria and methods developed by the Cochrane Back Review Group<sup>22</sup> and cohort studies will be evaluated using criteria developed by the U.S. Preventive Services Task Force.<sup>23</sup> Systematic reviews will be assessed using the AMSTAR quality rating instrument.<sup>20</sup> These criteria and methods will be used in conjunction with the approach recommended in AHRQ Methods Guide.<sup>19</sup> Studies

will be rated as “good,” “fair,” or “poor.” We will re-review the quality ratings of studies included in the prior American Pain Society review to insure consistency in quality assessment.

Primary studies rated “good” will be considered to have the least risk of bias, and their results will be generally considered valid. Good-quality studies use valid methods to select patients for inclusion and allocate patients to treatment; report similar baseline characteristics in different treatment groups; clearly report attrition and have low attrition; use appropriate methods to reduce performance bias, for example, blinding of patients, care providers, and outcome assessors; and use appropriate analytic methods, for example, intention-to-treat analysis and, for cohort studies, adjustment for potential confounders (which may include demographics or social and behavioral factors).

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

Studies rated “poor” will have significant flaws that imply biases of various types that may invalidate the results. They will have a serious or “fatal” flaw in design, analysis, or reporting, such as inadequate methods for allocating patients to treatment; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies will be least as likely to reflect flaws in the study design as the true difference between the compared interventions. We will not exclude studies rated as being poor in quality *a priori*, but poor-quality studies will be considered to be less reliable than higher quality studies when synthesizing the evidence, particularly when discrepancies between studies are present.

For systematic reviews, we will only include studies rated “good,” based on use of multiple sources in the literature search, application of pre-defined inclusion and exclusion criteria, assessment of risk of bias 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 consensus.

## **E. Data Synthesis**

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

question. In the evidence tables, we will include relevant studies from the prior ACP/APS review as well as new studies identified in current searches. We will summarize findings from prior good-quality systematic reviews, including the number and types of studies included and overall findings, separately from newly identified studies.

We will synthesize data qualitatively (based on ranges and descriptive analysis, with interpretation of results) and quantitatively (meta-analysis) when appropriate. Meta-analyses will be conducted to summarize data and obtain more precise estimates on outcomes for which studies are homogeneous enough to provide a meaningful combined estimate. The feasibility of a quantitative synthesis will depend on the number and completeness of reported outcomes and a judgment of adequate homogeneity among the reported results. In general, we would pool if three or more trials were available for a specific comparison and outcome; pooling would only be considered for two trials with high clinical homogeneity and low statistical heterogeneity. To determine whether meta-analysis could be meaningfully performed, we will consider the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes, and may conduct sensitivity analyses. We will consider using meta-analysis results from good-quality systematic reviews that used appropriate methods for pooling. 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. Meta-regression may be conducted to explore statistical heterogeneity using patient demographics, comorbidities, pain types, 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) given the availability of at least six to ten studies for continuous variables and four studies for categorical variables.<sup>24</sup>

Results will be presented as structured by the key questions and organized by the duration of symptoms (acute, subacute, or chronic) type of low back pain (non-radicular low back pain, radicular low back pain, spinal stenosis), with prioritized outcomes (pain, function) presented first.

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

The strength of evidence for each key question will be initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.<sup>19</sup> To ensure consistency and validity of the evaluation, the grades will be reviewed by the entire team of investigators for:

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

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).

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

- High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

## **G. Assessing Applicability**

Applicability will be assessed by examining the characteristics of the patient populations (e.g., demographic characteristics, duration or severity of low back pain, 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; methods for administration); and clinical settings (e.g., primary care, specialty setting; developing country versus developed country) in which the studies are performed. Issues with applicability may limit the ability to generalize the results to other populations and settings.

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## **VI. Definition of Terms**

None.

## **VII. Review of Key Questions**

AHRQ posted the key questions on the Effective Health Care Web site for public comment. The EPC refined and finalized the key questions after review of the public comments and input from Key Informants. This input is intended to ensure that the key questions are specific and relevant. Further input will be obtained from a Technical Expert Panel assembled for the systematic evidence review.

## **VIII. 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 TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **IX. Technical Experts**

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise

and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend 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 TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **X. 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.

## **XI. 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.

## **XII. Role of the Funder**

This project was funded under Contract No. HHS A 290-2012-00014-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.