Evidence-based Practice Center Systematic Review Protocol

Project Title: Treatments for Acute Episodic Migraine

Initial Publication Date: January 8, 2020
Amendment Date: January 9, 2020
(Amendments Details-see Section VII)

I. Background and Objectives for the Systematic Review

Migraine is best conceptualized as a chronic neurological disorder punctuated by recurrent attacks of headache and other symptoms such as photophobia, phonophobia, nausea and vomiting. It is one of the most common neurologic disorders affecting 12% of the general population and is ranked as the 7th highest cause worldwide of years lost due to disability. Despite the high prevalence of migraine and significant impact on patients’ lives, there are a number of barriers to patients obtaining appropriate migraine management, only 26.3% of patients with episodic migraine obtain appropriate acute migraine treatment.

The goals of acute treatment are to provide reliable and effective symptom relief as quickly as possible with minimal side effects so that patients can resume their daily activities without symptom recurrence. In patients with migraine, several acute treatment options are available, including opioid therapy, nonopioid pharmacologic therapy, and nonpharmacologic therapy. Guidelines list all triptans and several NSAIDs as first line acute treatments, as well as acetaminophen for non-incapacitating attacks. The evidence supporting triptans and NSAIDs is of high quality and has been established. In contrast, the evidence supporting the use of opioids, other nonopioid pharmacologic therapy, and nonpharmacologic therapies remain unclear. Therefore, patients and clinicians struggle when deciding when to use these therapies (other than triptans and NSAIDs). They also need information about the comparative effectiveness of these additional therapies to the first line treatments of triptans and NSAIDs.

In addition to effectiveness, decisionmakers need information on potential adverse risks, and special considerations in patients who may have certain co morbidities (e.g. kidney disease, sleep disordered breathing, mental illness) or other characteristics (e.g. older population, pregnant/breastfeeding women, patients with history of drug abuse/misuse/overdose).

The acute treatment of migraine presents unique challenges that differentiate it from other pain conditions. Frequent use of acute pharmacologic treatments carries the risk of medication overuse headache (MOH), which is considered a secondary headache and a complication of frequent migraine attacks. MOH is operationally defined based on headache frequency (15 or more days per month for greater than 3 months) and days of use per month of specific medications. Triptans, ergots alkaloids, combination analgesics, or opioids on 10 or more days per month meets criteria for medication overuse. However, simple analgesics including
nonsteroidal anti-inflammatory drugs (NSAIDs) used on 15 or more days per month, meets criteria for medication overuse. In addition, use of more than one class of medications, for example a triptan and an NSAID, on 10 or more days per month also meets criteria for MOH.

Acute treatment options do not have an equal risk of MOH development. Opiates and butalbital-containing medications have a two-fold higher risk of MOH development compared to simple analgesics and triptans. For this reason, the American Headache Society has explicitly stated that opioids and butalbital-containing drugs should not be used as first-line treatment for migraine and other recurrent headache disorders, and guidelines recommend that triptans and simple analgesics should be tried first. Additionally, the use of opioids for the acute treatment of migraine has been identified as a risk factor for disease chronification. Despite concern with use of opioids for migraine management, they are still often prescribed across all age groups.

Purpose of the review
This systematic review will address the critical evidence gaps and decisional dilemma by assessing the comparative effectiveness and harms for acute migraine treatments, including opioid therapy, nonopioid pharmacologic therapy, and nonpharmacologic therapy.

II. The Key Questions (KQ)

For patients with acute episodic migraine

KQ 1. Opioid therapy

KQ1a. What is the comparative effectiveness of opioid therapy versus: 1) nonopioid pharmacologic therapy (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], triptans, ergots alkaloids, combination analgesics, muscle relaxants, anti-nausea medications, and marijuana/cannabis) or 2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture, biofeedback, neuromodulatory devices) for outcomes related to pain, function, pain relief satisfaction, and quality of life and after follow-up at the following intervals: < 1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ1b. How does effectiveness of opioid therapy vary depending on: (1) patient demographics (e.g. age, race, ethnicity, gender, socioeconomic status [SES]); (2) patient medical comorbidities (previous opioid use, body mass index [BMI]); (3) dose of opioids; (4) duration of opioid therapy, including number of opioid prescription refills and quantity of pills used?

KQ1c. What are the harms of opioid therapy versus nonopioid pharmacologic therapy, or nonpharmacologic therapy with respect to: (1) misuse, opioid use disorder, and related outcomes; (2) overdose; (3) medication overuse headache (MOH), (4) other harms including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?
KQ1d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities; (3) the dose of opioid used; (4) the duration of opioid therapy?

KQ1e. What are the effects of prescribing opioid therapy versus not prescribing opioid therapy for acute episodic migraine pain on 1) short-term (<3 months) continued need for prescription pain relief, such as need for opioid refills, and 2) long-term opioid use (3 months or greater)?

KQ1f. For patients with acute episodic migraine being considered for opioid therapy, what is the accuracy of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?

KQ1g. For patients with acute episodic migraine being considered for opioid therapy, what is the effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?

KQ1h. For patients with acute episodic migraine being considered for opioid therapy, what is the effect of the following risk mitigation strategies on the decision to prescribe opioids: (1) existing opioid management plans; (2) patient education; (3) clinician and patient values and preferences related to opioids; (4) urine drug screening; (5) use of prescription drug monitoring program data; (6) availability of close follow-up?

**KQ 2. Nonopioid pharmacologic therapy**

KQ2a. What is the comparative effectiveness of nonopioid pharmacologic therapy (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], triptans, ergots alkaloids, combination analgesics, muscle relaxants, anti-nausea medications, and marijuana/cannabis) versus: 1) other nonopioid pharmacologic treatments, such as those in a different medication class; or 2) nonpharmacologic therapy for outcomes related to pain, function, pain relief satisfaction, and quality of life after follow-up at the following intervals: < 1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ2b. How does effectiveness of nonopioid pharmacologic therapy vary depending on: (1) patient demographics (e.g. age, race, ethnicity, gender); (2) patient medical comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) duration of treatment?

KQ2c. What are the harms of nonopioid pharmacologic therapy versus other nonopioid pharmacologic therapy, or nonpharmacologic therapy with respect to: (1) misuse,(2) overdose; (3) medication overuse headache (MOH), (4) other harms including gastrointestinal-related harms, cardiovascular-related harms, kidney-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cognitive harms, and psychological harms (e.g., depression)?

KQ2d. How do harms vary depending on: (1) patient demographics (e.g. age, gender); (2) patient medical comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) the duration of therapy?
KQ 3. Nonpharmacologic therapy

KQ3a. What is the comparative effectiveness of nonpharmacologic therapy versus sham treatment, waitlist, usual care, attention control, and no treatment after follow-up at the following intervals: < 1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ3b. What is the comparative effectiveness of nonpharmacologic treatments (e.g. exercise, cognitive behavioral therapy, acupuncture, biofeedback, neuromodulatory devices) for outcomes related to pain, function, pain relief satisfaction, and quality of life?

KQ3c. How does effectiveness of nonpharmacologic therapy vary depending on: (1) patient demographics (e.g. age, gender); (2) patient medical comorbidities?

KQ3d. How do harms vary depending on: (1) patient demographics (e.g. age, gender); (2) patient medical comorbidities; (3) the type of treatment used; (4) the frequency of therapy; (5) the duration of therapy?
### Table 1. PICOTS

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<tr>
<th>PICOTS Elements</th>
<th>Inclusion Criteria</th>
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| **Population**  | • Patients with acute episodic migraine seeking abortive treatment  
• Adults 18 years and older  
  *Special populations:*  
  o General adult  
  o Older populations >65 years  
  o Patients with history of substance use disorder  
  o Patients currently under treatment for opioid use disorder with opioid agonist therapy or naltrexone  
  o Patients with a history of mental illness  
  o Patients with history of overdose  
  o Pregnant/breastfeeding women  
  o Patients with comorbidities (e.g., kidney disease, sleep disordered breathing)  | • Animals  
* • Children (age < 18 years) |
| **Interventions** | KQ 1 a-e: Any systemic opioid abortive therapy, include:  
  • Codeine  
  • Fentanyl (Actiq, Duragesic, Fentora, Abstral, Onsolis)  
  • Hydrocodone (Hysingla, Zohydro ER)  
  • Hydrocodone/acetaminophen (Lorcet, Lortab, Norco, Vicodin)  
  • Hydromorphone (Dilaudid, Exalgo)  
  • Meperidine (Demerol)  
  • Methadone (Dolophine, Methadose)  
  • Morphine (Kadian, MS Contin, Morphabond)  
  • Oxycodone (OxyContin, Oxaydo)  
  • Oxycodone and acetaminophen (Percocet, Roxicet)  
  • Oxycodone and naloxone  
  • And other agonists, partial agonists and mixed mechanism opioids  

KQ 1 f-g: Instruments and genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose  

KQ 1 h: Risk mitigation strategies, including  
  • Existing opioid management plans  
  • Patient education  
  • Clinician and patient values and preferences related to opioids  
  • Urine drug screening  
  • Use of prescription drug monitoring program data  
  • Availability of close follow-up  
  • And others  

KQ 2: Any oral, injection, infusion, topical nonopioid abortive drug, including:  
  • Acetaminophen  
  • Nonsteroidal anti-inflammatory drugs [NSAIDs] (if compared against active treatment)  | For all KQs, exclude invasive treatments, and preventive (prophylactic) treatment  
* For KQ2, exclude NSAIDs vs placebo and triptans vs placebo
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<tr>
<th>PICOTS Elements</th>
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|                 | • Triptans (if compared against active treatment)  
|                 | • Ergots alkaloids  
|                 | • Combination analgesics  
|                 | • Muscle relaxants  
|                 | • Anti-nausea medications  
|                 | • Marijuana/cannabis  
|                 | • And others |
| KQ 3:           | Any non-invasive nonpharmacologic abortive therapy, including:  
|                 | • Exercise  
|                 | • Cognitive behavioral therapy  
|                 | • Acupuncture  
|                 | • And others |
| Comparators     | KQ 1: a-e. Usual care, another opioid therapy, nonopioid pharmacologic therapy, nonpharmacologic therapy  
|                 | KQ 1 f. Reference standard for misuse, opioid use disorder, or overdose; or other benchmarks  
|                 | KQ g-h. Usual care  
|                 | KQ 2: Another nonopioid pharmacologic therapy, nonpharmacologic therapy  
|                 | KQ3: Sham treatment, waitlist, usual care, attention control, and no treatment, another non-invasive nonpharmacologic therapy |
| Outcomes        | KQ 1. Opioid Therapy:  
|                 | KQ 1a-e. Pain, function, pain relief satisfaction and quality of life, harms/adverse events (including withdrawal, risk of misuse, opioid, OUD, overdose, MOH).  
|                 | KQ 1f. Measures of diagnostic accuracy  
|                 | KQ 1g-h. Misuse, opioid use disorder, overdose and other harms  
|                 | KQ 2. Non-Opioid Therapy:  
|                 | Pain, function, pain relief satisfaction, quality of life, and quality of life, harms/adverse events  
|                 | KQ 3: Non-invasive non-pharm Therapy:  
|                 | Pain, function, pain relief satisfaction, quality of life and quality of life, harms, adverse events |
| Timing          | At the following intervals: < 1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks | None |

None
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<tr>
<th>PICOTS Elements</th>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Settings</td>
<td>ER, physician’s office, hospital</td>
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<tr>
<td>Study design</td>
<td>• Original studies&lt;br&gt;  o RCTs&lt;br&gt;  o Comparative observational studies&lt;br&gt;  • Any sample size&lt;br&gt;  • Relevant systematic reviews, or meta-analyses (used for identifying additional studies)</td>
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<tr>
<td>Publications</td>
<td>Studies published in English only.</td>
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In vitro studies, non-original data (e.g. narrative reviews, editorials, letters, or erratum), single-arm observational studies, case series, qualitative studies, cost-benefit analysis, cross-sectional (i.e., non-longitudinal) studies, before-after studies, survey

Abbreviations: KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial
III. Analytic Framework

Figure 1. Draft analytic framework for Key Questions 1-3

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review: We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1).

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions: We plan to conduct a comprehensive database search, including Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, PsycINFO, and Scopus from database inception to the present. We have developed a preliminary database search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We will use relevant systematic reviews and meta-analysis to identify additional existing and new literature. We will also search FDA, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ’s Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. The search strategy will be peer-reviewed by an independent information specialist. An experienced librarian will
conduct the search. All citations identified through the process will be imported to a reference management system (EndNote® Version X9; Thomson Reuters, Philadelphia, PA). In addition, a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal will be available to collect additional study-specific information from industry stakeholders, professional societies, and researchers. A Federal Register Notice will be posted for this review.

Independent reviewers, working in pairs, will screen the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer will be retrieved for full-text screening. Independent reviewers, again working in pairs, will screen the full-text version of eligible references. Discrepancies between the reviewers will be resolved through discussions and consensus. If consensus can’t be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process.

**Data Abstraction and Data Management:** At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (author, year, study design, inclusion and exclusion criteria, patient characteristics, intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form will be pilot-tested by all study team members using 10 studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. A second reviewer will review data extraction, and resolve conflicts. In case that the included studies do not report all necessary information (e.g., methods and results), we will contact authors directly. DistillerSR will also be used to create data extraction forms and facilitate data extraction.

**Assessment of the Risk of Bias of Individual Studies:** We will evaluate the risk of bias of the included RCTs using the Cochrane Collaboration’s Risk of Bias 2 tool to assess bias from the randomization process, intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources. For observational studies, we will select appropriate items from the Newcastle-Ottawa Scale. We plan to use the QUADAS-2 tool for studies evaluating instruments for risk of opioid misuse, opioid use disorder, or overdose (KQ 1f). Additional criteria will be adopted from other quality appraisal tools if deemed necessary.

**Data Synthesis** - We will qualitatively summarize key features/characteristics (e.g. study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for each KQs.

We will determine whether meta-analysis is appropriate (i.e., more than 2 studies address the same PICOTS and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. If meta-analysis is deemed appropriate, we plan to use the profile likelihood random effect method to combine direct comparisons between treatments if the number of studies included in the analysis is larger than 3. In case that the profile likelihood method does not converge, we will use the DerSimonian-Laird random effect model with Hartung-Knapp-
Sidik-Jonkman variance correction. The fixed effect method based on the Mantel and Haenszel method will be adopted when the number of studies is 3 or less. We will evaluate heterogeneity between studies using $I^2$ indicator. To further explore heterogeneity, we plan to conduct subgroup analyses based on length of followup (< 1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks), patient demographics (e.g. age, race, ethnicity, gender, socioeconomic status (SES)), patient medical comorbidities (previous opioid use, body mass index (BMI)), dose/frequency of treatment, type of treatment, and treatment duration. We will conduct sensitivity analyses to evaluate robustness of our findings by excluding studies with high risk of bias.

To classify the magnitude of effects for pain and function, we plan to use the following rule:

Small/slight effect – A mean difference of 5 to 10 points on a 0- to 100-point visual analog scale (VAS), a standardized mean difference (SMD) of 0.2 to 0.5.

Moderate effect – A mean difference of 10 to 20 points on a 0- to 100-point VAS, a SMD of 0.5 to 0.8.

Large/substantial effect – Any value greater than moderate.

Similar thresholds will be used for other outcomes measures.

We will evaluate potential publication bias by evaluating funnel plots symmetry and using statistical tests such as Egger linear regression test if the number of studies included in a direct comparison is large (n>=10).

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: We will grade the strength of the body of evidence (SOE) as per the EPC methods guide on assessing SOE. RCTs start as high SOE. The domains to be used for all KQs will be: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

We will lower SOE grading when sensitivity analyses 1) show substantial difference in estimates derived from high or unclear risk of bias studies vs. estimates derived from studies at low risk of bias; or 2) when all the available studies (in a particular comparison) have high or unclear risk of bias. SOE grading will be also lowered when important heterogeneity is identified.

Based on this assessment and the initial study design, we will assign SOE rating as high, moderate, low, or ‘insufficient evidence to estimate an effect’.

High - We are very confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable).
Moderate - We are moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable).

Low - We have limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable).

Insufficient - We have no evidence, are unable to estimate an effect, or have no confidence in the estimate of effect.

We will produce summary of evidence tables that will provide for each comparison and for each outcome: data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating.

Assessing Applicability: We will follow the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies. 28 Applicability for each outcome will be summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. The following factors that may affect applicability have been identified, including patient factors (e.g., demographic characteristics (age, race, ethnicity, gender, SES), patient medical comorbidities (e.g., previous opioid use, BMI), intervention factors (e.g., dose/frequency of treatment, type of treatment, and treatment duration), comparisons (e.g., type of comparators), outcomes (e.g., use of unvalidated or nonstandardized outcomes), settings, and study design features (e.g., observational studies, RCTs). We will use this information to evaluate applicability of the evidence to real-world clinical practice in typical U.S. settings. We will report any limitations in applicability of individual studies in evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

V. References
15. Opioid Use Among People with Migraine: Results of the OVERCOME Study. HEADACHE; 2019. WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 59.

VI. Summary of Protocol Amendments

<table>
<thead>
<tr>
<th>Date</th>
<th>Section</th>
<th>Original Protocol</th>
<th>Revised Protocol</th>
<th>Rationale</th>
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<tr>
<td>January 9, 2020</td>
<td>IV. Method, Searching for the Evidence</td>
<td>For all interventions, we plan to conduct a comprehensive database search.</td>
<td>An overview of systematic reviews approach (also called umbrella systematic review) will be utilized to synthesize the evidence for triptans and NSAIDs. If more than one systematic review is available per drug, we will choose the most recent and inclusive one of high credibility.</td>
<td>Numerous systematic reviews that summarized evidence supporting the use of triptans and NSAIDs have been published. Another rationale for this approach is that triptans and NSAIDs are already recommended as a standard of care in clinical practice.</td>
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<td>Date</td>
<td>Section</td>
<td>Description</td>
<td>New Information</td>
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<td>January 9, 2020</td>
<td>IV. Method, Data Abstraction and Data Management</td>
<td>No specific methods were presented for conducting the overview of systematic reviews.</td>
<td>To synthesize the evidence from existing systematic reviews for triptans and NSAIDs, We will not update the literature searches of published systematic reviews; however, several systematic reviews have reported on several updates that demonstrated stability of the literature and evidence base, and suggested that future trials about the same comparisons were less likely to be conducted. Results will be presented narratively. We added methods to abstract and manage data from existing systematic reviews related to triptans and NSAIDs.</td>
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<tr>
<td>January 9, 2020</td>
<td>IV. Method, Assessment of the credibility of systematic reviews</td>
<td>None</td>
<td>For systematic reviews evaluating triptans or NSAIDs, we will use the AMSTAR tool (A measurement tool to assess systematic reviews) to assess the credibility of these systematic reviews. The tool evaluates 11 items: a priori protocol, duplication of reviewers, grey</td>
<td>We added methods to assess the credibility of systematic reviews.</td>
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VII. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.
Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

IX. 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.

X. Role of the Funder

This project was funded under Contract No. HHSA290201500013I 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.

XI. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).