

## Evidence-based Practice Center Systematic Review Protocol

Project Title: Diagnosis and Treatment of Insomnia Disorder

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

Adults around the globe struggle to achieve an appropriate duration and quality of sleep. Sleep difficulties are one of the most common complaints for adults in primary care.<sup>1</sup> These difficulties, associated with a decline in overall health status and perception of poor health, can have negative personal and social consequences.<sup>2</sup>

In the literature, the term insomnia can describe a symptom and/or a disorder and definitions used are not consistent. Individuals with insomnia report higher levels of anxiety, physical pain and discomfort, and cognitive deficiencies than those without sleep problems.<sup>3</sup> Insomnia may be associated with long-term health consequences such as increased morbidity, respiratory disease, rheumatic disease, cardiovascular disease, cerebrovascular conditions, and diabetes.<sup>2</sup>

Estimates of the annual costs of insomnia in the United States range between \$30 and \$107 billion.<sup>4</sup> These include direct costs of \$12 – \$14 billion for expenses such as medical appointments, over-the-counter sleep aids, and prescription medication. The remainder includes indirect costs such as lost productivity due to absenteeism and presenteeism (attending work while sick, fatigued), reduced quality of life, and accidents and injuries.

Insomnia involves dissatisfaction with sleep quantity or quality. It is associated with one or more of the following subjective complaint(s): difficulty with sleep initiation, difficulty maintaining sleep, or early morning waking with inability to return to sleep.<sup>5</sup> For an insomnia disorder diagnosis according to the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-5),<sup>5</sup> these symptoms must cause clinically significant distress or impairment(s) in functioning (social, occupational, educational, academic, behavioral or other) and occur despite adequate opportunity for sleep on at least 3 nights per week for at least three months. Additionally, the diagnosis requires that symptoms not be better explained by other sleep disorders or occur exclusively during the course of another sleep-wake disorder (narcolepsy, breathing-related sleep disorder, circadian rhythm disorder); not be attributable to the physiological effects of a substance; and not be explained by coexisting mental disorders or medical conditions. Dysfunction that can accompany insomnia disorder includes fatigue, poor cognitive function, mood disturbance, and distress or interference with personal functioning.<sup>1, 6</sup>

Prevalence estimates of insomnia vary by how the condition is defined. Estimates range from nearly 33 percent in an international sample of primary care patients to 17 percent of U.S. adults reporting "regularly having insomnia or trouble sleeping in the past 12 months" to 6 – 10 percent of adults meeting established diagnostic criteria.<sup>1, 5-7</sup> Previous diagnostic criteria for insomnia did not specify a minimum timeframe for sleep difficulties; chronic insomnia was used to describe cases that lasted from weeks to months, and insomnia was considered chronic in 40 – 70 percent of cases.<sup>6</sup>

Older adults and women have higher prevalence of insomnia and about half of insomnia cases coexist with a psychiatric diagnosis.<sup>8</sup> Aging is often accompanied by changes in sleep patterns (disrupted sleep, frequent waking, early waking) that can lead to insomnia.<sup>9</sup> Women are 1.4 times more likely than men to suffer from insomnia.<sup>10</sup>

Despite the condition's prevalence, patients may not discuss insomnia with primary care or general mental health providers, who may have little training in identifying and treating the disorder.<sup>11</sup> Additionally, the use of established diagnostic criteria in these settings is not known, and failure to use standard diagnostic criteria could lead to inappropriate treatment and/or delayed diagnosis of other medical or sleep disorders. For treatments to be effective, an accurate diagnosis must first be made.

Sleep medicine clinics diagnose insomnia according to criteria established by the International Classification of Sleep Disorders (ICSD) to diagnose insomnia. The Statistical Manual of Mental Disorders (DSM) diagnostic criteria is also frequently used in the United States and geared towards primary care and general mental health providers. Diagnostic criteria continue to evolve with advances in practice and research. Both criteria recognize sleep-related complaint(s) despite adequate opportunity for sleep combined with distress or dysfunction created by the sleep difficulty. Until recently, diagnostic criteria classified insomnia as primary or comorbid, depending on the absence or presence of other conditions. However, the most recent criteria describe in DSM-5 uses "insomnia disorder" and removed the distinction between primary and comorbid insomnia.<sup>5</sup> The distinction had questionable relevance in clinical practice, and revisions reflect this understanding by suggesting a diagnosis of insomnia disorder for patients who meet diagnostic criteria, despite any coexisting conditions. International of Sleep Disorders (ICSD-III) criteria to be released in 2014 will be consistent with the changes in DSM-5.

Other sleep-wake disorders can co-occur with insomnia and/or present with similar symptoms. As required by the DSM-5 insomnia disorder criteria, providers should rule out or diagnose these sleep-wake disorders in order to select an appropriate course of treatment.<sup>8</sup> For example, circadian rhythm disorder involves a discrepancy between circadian rhythms and sleep-wake cycles and often presents with sleepiness.<sup>8</sup> Other sleep disorders should also be considered during evaluation of sleep complaints, including breathing-related sleep disorders, restless legs syndrome, narcolepsy, and parasomnias.<sup>5, 8</sup> Insomnia disorder diagnosis is contingent upon ruling out other sleep, medical, or mental health disorders that explain the sleep problems.

Individuals suffering from sleep problems tend to seek treatment when symptoms become bothersome (e.g., distress, fatigue, daytime functioning, cognitive impairment).<sup>4</sup> Once insomnia disorder is accurately diagnosed, many treatments are available (Table 1). These include over-the-counter medications and supplements, education on sleep hygiene and recommended lifestyle changes, behavioral and psychological interventions, prescription medications, and complementary and alternative (CAM) treatments.

Insomnia is often treated with prescription medication. Several prescription medications are FDA approved for the treatment of insomnia (doxepin, triazolam, estazolam, temazepam, flurazepam, quazepam, zaleplon, zolpidem, eszopiclone, ramelteon). Several other prescription medications from various drug classes (e.g., antidepressants, antipsychotics) are used off-label.

American Academy of Sleep Medicine (AASM) guidelines describe treatment goals, including reduction of sleep and waking symptoms and improvement in daytime functioning.<sup>12</sup> These guidelines stress the importance of identifying and treating coexisting conditions. Various treatment options described in the guidelines include psychological and behavioral interventions, drugs, and combined approaches.<sup>12</sup> AASM practice parameters state that psychological and behavioral interventions are effective and recommended for primary chronic insomnia and secondary insomnia (ICSD-II criteria) in adults.<sup>13</sup> Recommendations were supported by the highest quality evidence.<sup>12</sup> Support for short-term use of pharmacological interventions was based on consensus.<sup>12</sup> However, an updated review of evidence synthesis and recommendations on these interventions is underway.<sup>14</sup> Combined or stepped care models have more recently been used in treatment (initiating one intervention followed by another modality) studied. Combination therapy specifies the timing of certain intervention components.<sup>15</sup> The stepped care model has been described in terms of how limited CBT therapies could be used.<sup>16</sup> These approaches are promising because they are designed to maximize treatment benefits while minimizing harms while assisting in efficient delivery of services at the level appropriate for the patient.

Treatment options are not limited to psychological and behavioral therapies and pharmacologic interventions. Efficacy research has been conducted on a variety of CAM approaches (Chinese herbal medicine, acupuncture, reflexology, Suanzaoren decoction, etc.). Unfortunately, methodological limitations have prevented conclusive evidence synthesis for these treatments.<sup>17-26</sup>

The evaluation of treatments for insomnia disorder may need to specifically address certain subpopulations (the elderly, adults with coexisting conditions prevalent among insomnia patients). Older age and coexisting conditions may complicate treatment, especially when drug interventions are used. The prevalence of insomnia is particularly high among individuals with existing psychiatric and chronic pain disorders.<sup>12</sup> Treatments may differ in these groups due to their enhanced susceptibility to medication harms, use of medications, and other potential confounders.

Insomnia treatment goals include meaningful improvements in sleep and associated distress and/or dysfunction. Improvements in sleep can be measured in a variety of ways. Because patient complaints can encompass specific symptoms such as sleep-onset latency, number of awakenings, wake after sleep onset, and total sleep time, these are often measured to assess efficacy or effectiveness. Sleep efficiency (total sleep time/total time in bed) is a broader sleep measure that may capture the net effect of specific sleep symptoms. Assessing improvements in specific sleep symptoms or in sleep efficiency can be measured objectively or subjectively. Sleep parameters are objectively measured with polysomnography (measuring sleep continuity parameters, sleep time spent in each stage) or actigraphy (measuring body movements). Subjective sleep symptoms that may cause significant distress are typically collected using sleep diaries. Despite discrepancies between objective and subjective measures of sleep parameters, the subjective measures are considered more valuable because they are patient-centered outcomes.

Sleep quality, subjectively measured in a variety of ways, is also an important measure. Additionally, a number of questionnaires have been developed to assess sleep and the impact on distress/dysfunction. Unfortunately, many currently available sleep

symptom questionnaires were developed to identify poor sleepers and are not adequately sensitive to detect clinically meaningful treatment effects.<sup>27</sup> Two important questionnaires that measure both constructs include the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Impact (ISI). Ideally, valid and reliable questionnaires that measure both constructs simultaneously; have the sensitivity to detect changes resulting from treatment; and measured and analyzed using clinically meaningful improvements would be valuable in demonstrating efficacy and effectiveness.

Insomnia has been shown to have a negative impact on emotional status and quality of life. Treatments can potentially improve secondary patient-centered outcomes such as mood and well-being, quality of life, and productivity. Questionnaires that measure these outcomes have also been used in insomnia efficacy and comparative effectiveness research (i.e., Short-form Health Survey [SF-36]<sup>12, 28</sup>; Sickness Impact Profile Scale<sup>28</sup>; World Health Organization Quality of Life [WHOQOL]<sup>28</sup>). The same psychometric and measurement issues apply to these outcome measurements.

**Table 1: Examples of Treatments for Insomnia in Adults Studied in the Literature**

<b>Treatment Category</b>	<b>Treatment</b>
Behavioral/psychological	Aroma therapy Bright-light therapy Brief behavioral therapy Biofeedback Cognitive behavioral therapy (CBT) Exercise Music therapy Relaxation training Sleep hygiene education Sleep restriction
CAM	Acupuncture Acupressure Cupping Homeopathy Hypnotherapy Reflexology Tai Chi Yoga
CAM – herbal/dietary supplements	Bach Flower Isoflavones L-tryptophan Magnesium Melatonin Valerian
<b>Medications<sup>6</sup></b>	
Medications - antihistamines	Diphenhydramine Doxylamine
Medications - Prescription antidepressants	Amitriptyline Doxepin* Trazodone Mirtazapine
Medications – Prescription antipsychotics	Olanzapine Quetiapine
Medications –Prescription hypnotics	<u>Benzodiazepines</u> Alprazolam Clonazepam Estazolam* Flurazepam* Lorazepam Quazepam* Temazepam* Triazolam* <u>Non-Benzodiazepines</u> Eszopiclone* Zaleplon* Zolpidem*
Medications - melatonin receptor agonist	Ramelteon*
Medications – Prescription antipsychotics	Gabapentin Pregabalin

Many systematic reviews and randomized controlled trials have examined the treatment of insomnia. The target audience for AASM guidelines is sleep medicine professionals. Other guidelines do target primary care audiences, such as recommendations on the assessment and management of insomnia in older adults.<sup>29</sup> Several recent international guidelines specifically address primary care providers.<sup>2, 8, 30, 31</sup> However, previous systematic reviews and guidelines may not have reached the broad audience of U.S.-based primary care providers.

Available reviews do not incorporate the broad range of interventions (psychological and behavioral, pharmacologic, CAM) or target guideline developers with the specific intention of improving the treatment of insomnia disorder in primary care and general mental health settings. Current guidance and evidence-synthesis would benefit from a comprehensive systematic review and recommendations aiming to improve management of insomnia disorder in adults in primary care settings. The objective of this review is to identify previous systematic reviews and randomized-controlled trials (RCTs) to provide a comprehensive up-to-date synthesis of the evidence on efficacy and comparative effectiveness of insomnia disorder treatments.

## II. The Key Questions

Preliminary Key Questions for this review were posted for public comment in October of 2013. We received several comments useful in revising the Key Questions to better address concerns of a wide variety of stakeholders in the most meaningful and efficient way.

Public comments suggested possible contamination by including studies that enroll patients with insomnia as well as other conditions. However, we believe that studies enrolling subjects with the wide variety of conditions (heart disease, diabetes, anxiety/depression and other chronic medical or psychiatric conditions) accurately reflect the patient population and we will include these. However, studies that strictly enroll subjects based upon a complex diagnosis in addition to insomnia, such as Parkinson's disease or post-traumatic stress disorder, will not be included because it is unclear whether these patients truly have insomnia disorder concurrent with their condition, or whether these patients have insomnia symptoms concomitant to their condition.

Respondents also expressed concern over the subjective nature of many of the outcomes and their associated measurement instruments. While patient-reported outcomes have disadvantages, they are patient-centered and represent the best way to assess improvements in response to treatment. By examining the marginal improvement over appropriate control conditions, we hope to better capture the treatment effect.

Question 1. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in adults?

- a. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in specific *subgroups of adults*?
- b. What are the efficacy and comparative effectiveness of *combined treatments* (e.g. *cognitive behavioral therapy and drug therapy*) for the treatment of insomnia disorder in adults?

- c. What are the *long-term* efficacy and comparative effectiveness of treatments for insomnia disorder in adults?

Question 2. What are the harms of treatments for insomnia disorder in adults?

- a. What are the harms of treatments for insomnia disorder in specific *subgroups of adults*?
- b. What are the harms of *combined treatments (e.g. cognitive behavioral therapy and drug therapy)* for insomnia disorder in adults?
- c. What are the *long-term* harms of treatments for insomnia disorder in adults?

## PICOTS

### Population(s)

Adults, age 18 and above, with insomnia disorder (i.e. insomnia definitions that match insomnia disorder diagnostic criteria)

- Specific subgroups:
  - older adults
  - adults with coexisting medical or mental health disorders (such as mild depression/anxiety, osteoarthritis)

**Intervention Categories (Table 1 lists examples of specific interventions in each category)**

- Behavioral/Psychological
- CAM
- CAM-herbs and supplements
- Pharmaceutical (available in the U.S.)

### Comparators

**KQ 2:** Placebo or active control; usual care; other insomnia treatment. Comparators for behavioral/psychological and non-supplement CAM interventions must be active control therapies.

### Outcomes

#### KQ1

#### Primary patient-centered outcomes

- Patient-reported sleep and/or distress/dysfunction:

*Measurement:* Assessments derived from sleep diaries (sleep-onset latency (SOL), number of awakenings (NOA), wake after sleep onset (WASO), total sleep time (TST), sleep efficiency [(TST) total sleep time/total time in bed], or questionnaires [Athens Insomnia Scale (ASI)<sup>28</sup>; Epworth sleepiness scale (ESS)<sup>12</sup>; Fatigue Severity Scale (FSS)<sup>12, 28</sup>; Glasgow Sleep Impact Index (GSII)<sup>32</sup>; Insomnia Severity Index (ISI)<sup>12, 28</sup>; Leeds Sleep evaluation questionnaire<sup>28, 36</sup>;

Multidimensional Fatigue Scale<sup>28</sup>; Patient-Reported Outcomes Information System (PROMIS)<sup>33</sup>; Pittsburgh Sleep Quality Index (PSQI)<sup>13, 28</sup>; Women's Health Initiative Insomnia Rating Scale (WHIIRS)<sup>35</sup>]

**Secondary patient-centered Outcomes**

- Mood/well-being and Quality of life

Measurement: Assessments derived from questionnaires: [Beck Depression Inventory (BDI)<sup>12, 28</sup>; State-Trait Anxiety Inventory (STAI)<sup>12, 28</sup>; Profile of Mood States<sup>28</sup>; Quality of Life/Functional Status; Clinical Global Impression Scale (CGIS)<sup>28</sup>; Short-form Health Survey (SF-36)<sup>12, 28</sup>; Sickness Impact Profile Scale<sup>28</sup>; World Health Organization Quality of Life (WHOQOL)<sup>28</sup>]

**KQ2**

Adverse effects of intervention(s)

1. Any serious adverse effects (e.g., dependence, falls, abnormal sleep behaviors, etc.)

**Timing**

KQ1: Outcomes measured at 4 weeks to 3 months after initiation of treatment will be used to assess efficacy/comparative effectiveness.

KQ1c. Follow-up measures beyond 3 months of treatment will be used to evaluate long-term efficacy and comparative effectiveness.

**Settings**

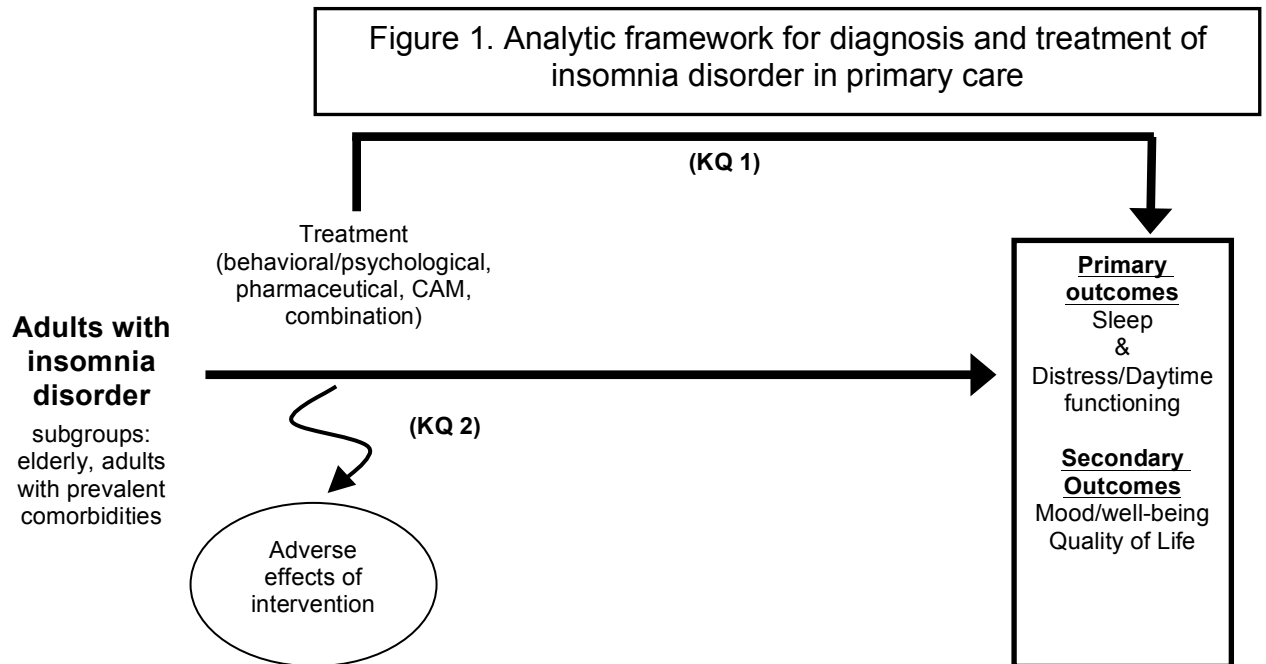
Any outpatient setting

**III. Analytic Framework**

Figure 1 provides an analytic framework to illustrate the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis.



## Draft Analytic Framework



## IV. Methods

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

Studies will be included or excluded in the review of treatments based on the PICOTS framework outlined in Section II and the study-specific inclusion criteria described in Table 2. Treatments for insomnia disorder in primary care settings will need to address certain subpopulations such as the elderly and adults with certain uncomplicated coexisting conditions prevalent among insomnia patients (i.e. osteoarthritis, depression and anxiety) specifically. Other medical or mental health conditions (e.g. pregnancy, menopause, major depressive disorder, bipolar disorder, post-traumatic stress disorder, fibromyalgia, rheumatoid arthritis, Parkinson's disease, etc.) deserve the attention of a separate review and are considered outside the scope of this review. These conditions are excluded because it is unclear these cases of insomnia accurately represented insomnia disorder or insomnia symptoms concomitant to their other diagnosis.

**Table 2. Study inclusion criteria**

Category	Criteria for Inclusion
Study enrollment	<ul style="list-style-type: none"><li>adults with diagnoses consistent with insomnia disorder:<ul style="list-style-type: none"><li>efficacy/comparative effectiveness: 4 weeks to 3 months</li><li>sustained efficacy/comparative effectiveness: over 3 months</li></ul></li><li>subgroups of adults:<ul style="list-style-type: none"><li>older adults</li><li>adults with insomnia disorder and coexisting medical or mental health diagnoses (i.e., depression/anxiety, osteoarthritis and other conditions prevalent among those with insomnia disorder and commonly treated in primary care settings)</li></ul></li></ul>
Study Design and Quality	<ul style="list-style-type: none"><li>Systematic reviews and RCTs</li></ul>
Publication type	<ul style="list-style-type: none"><li>Published in peer reviewed journals.</li></ul>
Language of publication	<ul style="list-style-type: none"><li>English</li></ul>

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

We will search Ovid Medline, Ovid PsycInfo, Ovid Embase, and the Cochrane Library to identify previous systematic reviews and randomized controlled trials published and indexed in bibliographic databases through November 2013. Our search strategy appears in Appendix A. Our search strategy will include relevant medical subject headings and natural language terms for the concept of insomnia. This concept was combined with filters to select RCTs and systematic reviews. Bibliographic database searches will be supplemented with backward citation searches of highly relevant systematic reviews. We will update searches while the draft report is under public/peer review.

Two independent investigators will review titles and abstracts of bibliographic database search results to identify systematic reviews and trials studying interventions for insomnia. Citations determined potentially eligible by either investigator will undergo

full text screening. Two investigators will independently screen full text to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator. We will document the inclusion and exclusion status of citations undergoing full-text screening.

We will conduct additional grey literature searching to identify relevant completed and ongoing studies. Relevant grey literature resources include trial registries and FDA databases. We will search ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP) for ongoing studies. We will also review Scientific Information Packets (SIPs) sent by manufacturers of relevant interventions. Grey literature search results will be used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and inform future research needs.

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

We will use data from relevant comparisons in previous systematic reviews to replace the de novo extraction process when the comparison is sufficiently relevant and the systematic review methodology is assessed as fair or good. Data from RCTs in included systematic reviews will not be separately extracted to avoid double-counting study results.

Remaining RCTs meeting inclusion criteria will be distributed among investigators for risk of bias assessment and data extraction. For studies assessed as having low to moderate risk of bias (according to methods described below), one investigator will extract relevant study, population demographic, and outcomes data. Data fields to be extracted will be determined based upon proposed summary analysis. These fields will include author, year of publication; setting, subject inclusion and exclusion criteria, intervention and control characteristics (intervention components, timing, frequency, duration), follow-up duration, participant baseline demographics, comorbidities; insomnia definition, method of diagnosis, and severity, descriptions and results of primary outcomes and adverse effects, and study funding source. Relevant data will be extracted into web-based extraction forms created in RedCap.<sup>34</sup> Data will be exported into Excel spreadsheets for descriptive analysis. Data will be analyzed in RevMan 5.2<sup>35</sup> software. Data appearing in final evidence tables will be verified for accuracy by one investigator.

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

Risk of bias of eligible systematic reviews will be assessed using modified AMSTAR criteria.<sup>36</sup> Two investigators will independently assess risk of bias for randomized controlled trials using questionnaires developed from the Cochrane Risk of Bias tool. The seven domains included in this tool include sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data (i.e., was incomplete outcome data adequately addressed), selective reporting, and other sources of bias (i.e., problems not covered by other domains). Additional items will be developed to assess potential risk-of-bias not addressed by the Cochrane tool. Outcomes measurement issues inherent in the psychometric properties of

the questionnaires used to measure outcomes and assessment methods used to detect change in those questionnaire results will be specifically evaluated for detection bias. Additional items may be necessary to evaluate potential risk-of-bias associated with treatment definition and implementation (treatment fidelity). Specific study methodology or conduct will be used to judge potential risk of bias with respect to each domain following guidance in the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0.<sup>37</sup> Overall summary risk of bias assessments for each study will be classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations. Investigators will consult to reconcile any discrepancies in overall risk of bias assessments. When the two investigators disagree, a third party will be consulted to reconcile the summary judgment. Outcomes in studies assessed as having a high risk of bias will be compared to synthesized evidence as a means of sensitivity analysis. Contradictions will be investigated in further depth.

### **E. Data Synthesis.**

We will summarize the results into evidence tables and synthesize evidence for each unique population, comparison, and outcome combination. When a comparison is adequately addressed by a previous systematic review of acceptable quality and no new studies are available, we will reiterate the conclusions drawn from that review. When new trials are available, previous systematic review data will be synthesized with data from additional trials.

We will summarize included study characteristics and outcomes in evidence tables. We will assess the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.<sup>38</sup> Populations included in the study, the interventions, and outcomes measured will need to be sufficiently similar before pooling data. If data are appropriate for pooling, meta-analysis will be performed.

Using a random effects model, we will calculate risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary primary outcomes. Weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs will be calculated for continuous outcomes.

We will assess statistical heterogeneity with Cochran's Q test and measure magnitude with  $I^2$  statistic.<sup>38</sup> When direct evidence on certain comparisons is not available, indirect comparison will be explored.<sup>38</sup> When pooling is not appropriate due to lack of comparable studies or heterogeneity, qualitative synthesis will be conducted.

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

The overall strength of evidence for primary outcomes within each comparison will be evaluated based on four required domains: (1) study limitations (risk of bias); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate).<sup>39</sup> A fifth domain, reporting bias, will be assessed when SOE based upon the first four domains is moderate or high.<sup>39</sup> Based on study design and conduct, risk of bias

will be rated as low, medium, or high. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study). Directness will be rated as either direct or indirect. Precision will be rated as precise or imprecise. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association. Based on these factors, the overall strength of evidence for each outcome will be rated as:<sup>39</sup>

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confidence that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

#### **G. Assessing Applicability.**

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, the population from which the study participants are enrolled (i.e., studies enrolling participants from sleep medicine clinics may not produce results applicable to the general population of patients being treated for insomnia in primary care clinics), narrow eligibility criteria, and patient and intervention characteristics different than those described by population studies of insomnia.<sup>40</sup> Specific factors that could modify the effect of treatment and affect applicability of findings include diagnostic accuracy, insomnia severity, and specific patient characteristics, such as age.

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## **VI. Definition of Terms**

Not applicable

## **VII. Summary of Protocol Amendments**

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

## **VIII. Review of Key Questions**

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions were posted for public comment and finalized by the EPC after review of the comments.

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

## **X. Technical Experts**

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or 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 contribute to the writing of the report and 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.

## **XI. Peer Reviewers**

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential 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 which cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

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

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