



## Evidence-based Practice Center Systematic Review Protocol

Project Title: Attention Deficit Hyperactivity Disorder (ADHD)

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(Amendments Details—see Section VII)

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

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder, with a prevalence that has increased since the 1990s.<sup>1</sup> In the United States, there are significant geographical variations in the rate of diagnosis and treatment.<sup>1</sup> The most recent *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*<sup>2</sup> has revised the diagnostic criteria. To be diagnosed with ADHD, a child or younger adolescent needs to meet 6 out of 9 possible inattentive symptoms (such as failing to give close attention to details or being easily distracted) and/or 6 out of 9 possible hyperactivity/impulsivity symptoms (such as being “on the go” or difficulty waiting their turn). Furthermore, symptoms need to be present for at least 6 months, occur in at least 2 different settings, be present before 12 years of age, and not be better explained by another disorder. For older adolescents and adults, the number of required symptoms per category is reduced to 5 out of 9. There are three presentations of ADHD: (1) predominantly inattentive, (2) predominantly hyperactive/impulsive, and (3) combined, based on how many symptoms in each diagnostic category an individual meets. The inattentive presentation is used when an individual meets the necessary inattentive symptom count but does not for hyperactivity/impulsivity and vice versa. The combined presentation is used when an individual meets the necessary symptom count for both.

The prevalence of ADHD has been increasing at a rate greater than 3% each year since 1997.<sup>1,3</sup> It is unclear what underlies this increase, including the degree to which it is caused by heightened awareness, changing diagnostic criteria, or misclassification. Medical management is considered a frontline treatment for ADHD, with the majority of treatments using FDA-approved psychostimulant medications that reduce core symptoms of the disorder. Specifically, psychostimulants are effective in reducing distractibility, improving sustained attention, reducing impulsive behaviors, and improving activity level. Nonpharmacologic therapies (e.g., behavioral therapy, psychotherapy, psychosocial interventions, and complementary and alternative medicine interventions) are also in common use and can potentially address core symptoms of ADHD or the functional impairments that are associated with the disorder.

Treatment in childhood is associated with improved reading achievement, decreased school absenteeism, and decreased grade retention.<sup>4</sup> ADHD is also associated with tobacco and other substance abuse, which may be modified with treatment.<sup>5,6</sup> However, stimulants themselves may also be misused. Overall, ADHD is associated with an increased risk of having other psychiatric comorbidities and to have an increased risk of mortality.<sup>7</sup>

As discussed below, there are important questions related to the diagnosis of ADHD, including how to assure appropriate diagnosis and avoidance of misdiagnosis; how to best tailor therapy to

individuals based on their characteristics (e.g., age, sex, ADHD symptoms, comorbid conditions, prior and current therapy); and how to efficiently and effectively monitor individuals with ADHD over time. Understanding of which populations are at greatest risk for ADHD and who is most likely to benefit from treatment is also evolving.

Population: According to the Centers for Disease Control and Prevention, 11% of children 4 through 17 years of age have been diagnosed with ADHD as of 2011; however, there is significant variation in diagnosis and treatment across states and communities.<sup>8,9</sup> In addition, the manifestation and impact of ADHD and the safety and effectiveness of therapy vary by age. Younger children with ADHD are more likely to be diagnosed with predominantly hyperactive/impulsive presentation or combined presentation, whereas the diagnosis of predominantly inattentive presentation is more common among older individuals. These differences are thought to be related to the typical developmental changes in attention span with increasing age and to the increasing demands for attention and focus in the later school age and adolescent period. Current treatment guidelines prioritize behavioral treatments over medication management in younger children. Accordingly, this review will focus on children through 17 years age. Although we will abstract specific age data, we plan to categorize age as less than 4, 4 through 6, 7 through 12, and 13 through 17. These age categories were chosen to reflect child and adolescent developmental stages. We will also explore the impact of ADHD and its treatment and monitoring strategies in several subgroups of interest. These include exploring findings by gender: boys are more likely than girls to be diagnosed. In addition, symptoms may also vary by sex, with girls more likely to be inattentive and boys more likely to be hyperactive and impulsive.<sup>10</sup> The degree to which these differences are due to referral bias or an underlying biological difference is unclear. Other risk factors that might affect identification and treatment include family history, prematurity, exposure to alcohol or other drugs *in utero*, other developmental disabilities or mental illness, and access to health care.<sup>11,12</sup> Studies that explore the comparative effectiveness of diagnostic strategies, treatments, or monitoring strategies within patients from these populations will be identified and synthesized.

Many risk factors have been associated with ADHD. These include prenatal factors (e.g., tobacco use, alcohol use, substance abuse), perinatal factors (e.g., low birth weight, prematurity), and early postnatal factors (e.g., lead exposure, social environment).<sup>13</sup> Also, family history of ADHD and specific genetic conditions (e.g., Fragile X syndrome) can be associated with ADHD. For this systematic review, we will focus on common risk factors that could affect diagnosis and treatment outcomes, including prenatal tobacco, alcohol, or substance abuse; prematurity or low birth weight; and family history.

ADHD Diagnosis: ADHD diagnosis is normally based on physician assessment to determine whether the patient meets the criteria described in the DSM-5, which is similar to the DSM-4 for the diagnosis in childhood. Rating scales, discussed below among the monitoring strategies, which can be completed by parents, teachers, and/or patients, are used to evaluate the presence of each of the 18 symptoms as well as the degree of impairment that results from symptoms. Rating scale data are integrated with a clinical interview to determine the onset, course, duration, and impairment associated with symptoms. In addition, screening and clinical evaluation of potential comorbid psychiatric conditions is a key part of the diagnostic process. Important questions remain about the accuracy of this approach in primary care settings. A particular challenge is separating ADHD from other conditions that may appear similar (e.g., anxiety, conduct

disorders, speech or language delay, other developmental disorders) and determining whether another condition may better explain ADHD symptoms or is present as a comorbid diagnosis.

The U.S. Food and Drug Administration (FDA) has approved the Neuropsychiatric Electroencephalograph [EEG]-Based Assessment Aid (NEBA; NEBA Health, Augusta, GA) “to aid in the diagnosis of ADHD” in patients 6-17 years of age. NEBA is used to provide clinical support but does not replace the clinical evaluation.<sup>14</sup>

Adverse Effects of Diagnosis: Being diagnosed with ADHD could potentially lead to “labeling harms,” which can lead to stigma, reduced self-esteem, or reduced future educational attainment or career opportunities.<sup>15-17</sup> Misdiagnosis can lead to overdiagnosis or underdiagnosis and can also miss conditions that can be similar in appearance to ADHD (e.g., anxiety, conduct disorders, speech or language delay, other medical disorders/diseases, or other developmental disorders).

Treatment Strategies: Treatment strategies for ADHD are diverse and can be divided into pharmacologic and nonpharmacologic therapies. The main categories of pharmacologic therapies include stimulants, selective norepinephrine reuptake inhibitors, alpha-2 agonists, and antidepressants. Nonpharmacologic therapies include psychosocial interventions, behavioral interventions, school interventions, cognitive training therapies, learning training, biofeedback or neurofeedback, parent behavior training, dietary supplements (e.g., omega-3 fatty acids, vitamins, herbal supplements, probiotics), elimination diets, vision training, and chiropractic treatment. The American Academy of Pediatrics (AAP) recommends stimulant therapy as the first line of therapy.<sup>18</sup> Recent studies have been inconsistent as to whether there is a significant benefit of combining behavioral therapy with stimulant therapy,<sup>19</sup> or whether nonpharmacologic therapy may be effective.<sup>20</sup> These uncertainties highlight the need for a systematic review of the evidence.

Monitoring Strategies with Intermediate Outcomes: After a child is diagnosed with ADHD and an initial treatment strategy is determined, a monitoring strategy is applied to ensure that outcomes are evaluated over time and modification to treatments are made when needed. Repeat monitoring allows intervention (e.g., change in treatment) before the final outcomes associated with ADHD occur. Several instruments are available to monitor treatment response and adverse effects over time, including the Vanderbilt scales, the Conner scales, and the SNAP-IV rating scales.<sup>21-23</sup> Monitoring also includes assessment of any adverse effects of treatment. There are variations in the frequency of monitoring, often based on the age of the child, the specific treatment, duration of treatment, previous symptoms and comorbid conditions, and family and health care provider preferences. Rating scale results are intermediate monitoring outcomes, associated with the outcomes described below.

Final Outcomes: Outcomes associated with having ADHD in childhood primarily are based on measures of performance and/or functional impairment. In childhood, individuals with ADHD are at risk for lower academic performance (e.g., grades, scores on standardized test), lower rates of graduation from high school, higher rates of grade retention, and higher rates of school suspension. In adulthood, outcomes may include limited workforce participation and/or difficulty maintaining a steady job. Throughout the lifespan, social outcomes associated with ADHD may include problematic peer and family relationships. Individuals with ADHD are at risk for negative outcomes associated with risk-taking behaviors such as motor vehicle collisions or other accidents as well as substance use (e.g., higher rates of smoking, more difficulty quitting smoking). Mental health outcomes that are associated with ADHD include higher rates of mood

disorders, depression or anxiety, higher likelihood of having self-injurious nonsuicidal behavior, suicide (attempted or completed), suicidal ideation, and risk of mortality. Assessment of these final outcomes is challenging because they can be related to the negative outcomes of ADHD, ADHD-related comorbidities, or ADHD treatment.

Adverse Effects of Treatment: Adverse effects associated with pharmacologic treatment can include changes in appetite, growth suppression,<sup>24</sup> weight decrease, sleep disturbance, gastrointestinal symptoms, elevated blood pressure, increased heart rate, risk of sudden cardiac death, cardiac arrhythmias, conduction abnormalities, tics or other movement disorders, behavior changes, hallucination, aggression, suicide (attempted or completed), and suicidal ideation. Suicide and suicidal ideation therefore can be both an adverse effect of treatment and an ADHD-related health outcome. Treatment can also lead to personality changes or perceived loss of spontaneity. Adverse effects of nonpharmacologic treatment depend on the specific intervention. These adverse effects are not likely to expand beyond those expected for pharmacologic therapy. Individuals who are initially misdiagnosed or who have inadequate monitoring may be overtreated. Overtreatment leads to risk of treatment with no or little potential benefit. Because many of the pharmacologic treatments are controlled substances, overtreatment could also lead to abuse of a drug to which the treated individual might not otherwise have access.<sup>25</sup> All treatments can potentially lead to parental stress, and depending on the specific treatment, there may be significant time demands or opportunity costs.

Timing, Setting, and Context: This review will focus on diagnosis and management of ADHD within the primary care practice setting or other setting in which care can be coordinated by primary care providers (e.g., in partnership with community-based psychologists or psychiatrists). Although treatment of ADHD in childhood and adolescence is the focus, the review will evaluate outcomes in adulthood from treatment that occurs during childhood or adolescence.

Rationale for an Evidence Review: This review updates a prior EPC review from 2011 that focused on the effectiveness of ADHD treatment in at-risk preschoolers, the long-term effectiveness of ADHD treatment in all ages, and the variability in ADHD prevalence, diagnosis and treatment.<sup>26</sup> This current review will update and build on that previous report and will address important gaps in knowledge related to the diagnosis of ADHD, concerns about overtreatment and undertreatment, and conflicting literature about the effectiveness of treatment. Regarding diagnosis, the DSM-5 has changed the criteria for ADHD. The criteria have been relaxed to allow some symptoms to appear prior to 12 years of age compared with 7 years of age, allowing more adolescents to fulfill the criteria. In addition, DSM-5 does not exclude the co-occurrence of autism spectrum disorder for the diagnosis of ADHD. Many treatment studies are based on small trials and do not take into account the DSM-5 criteria. The significant geographic variations in care likely reflect differences and uncertainty in care delivery. Inappropriate diagnosis can lead to undertreatment, overtreatment, or missed diagnosis of other conditions.

The DSM-5 criteria emphasize the life-long, chronic nature of ADHD and the need to monitor individuals over time. However, the optimal strategy for monitoring or treatment is unclear. There may be a difference in treatment effectiveness between males and females and among at-risk individuals.

Patient Preferences: There are differences in patient and family preferences related to both pharmacologic and nonpharmacologic treatment<sup>27</sup> and potential outcomes. These treatment

preferences have been shown to be associated with treatment initiation and choice. Findings from this planned systematic review will help inform patient and family decisions based on the benefit and harm of specific treatments and the parents' preferences for those different outcomes.

Cost: Pharmacologic treatments vary significantly in cost. The older but short-acting stimulants are the least expensive. Nonpharmacologic therapy, including behavioral interventions, can be costly for patients and families. Although we have not included cost as an explicit outcome of interest, future decisionmakers could incorporate our effectiveness findings into their cost analysis to determine the potential cost effectiveness of alternative strategies.

Other Contextual Factors: Since the most recent AAP practice guideline based on a systematic review was published in 2011, four new medications have become available (methylphenidate transdermal system, lisdexamfetamine, amphetamine sulfate tablets, and dextroamphetamine sulfate tablets), and the DSM-5 has been released, increasing clinical and decisionmaking uncertainty. Concerns remain about both overtreatment and undertreatment of ADHD. A separate EPC report on disruptive behavior disorder is nearly complete, and therefore will not be targeted in this evidence review. However, disruptive behavior specifically related to ADHD will be included.

## II. The Key Questions

The draft key questions (KQs) developed during Topic Refinement were available for public comment from June 17, 2015, to July 8, 2015. The public comments focused on expanding the age range to include all children through 17 years of age, adding diversion of pharmacotherapy as a risk of treatment, expanding the potential adverse effects of treatment considered, adding incarceration or other interactions with the legal system (juvenile detention, probation, court-mandated interventions, need for residential placement) as an outcome, stratifying findings by clinical setting (e.g., primary care, specialty clinic), and improving the description of the risk of labeling and misdiagnosis. The KQs were revised in response to these comments. Overall, the comments affirmed our planned approach. There were no other significant changes to the KQs or proposed methods.

KQ 1: What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals through 17 years of age?

- a. How does the comparative diagnostic accuracy of these approaches vary by clinical setting, including primary care or specialty clinic, or patient subgroup, including age, sex, or other risk factors associated with ADHD?
- b. What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD?

KQ 2: What are the comparative safety and effectiveness of pharmacologic and/or nonpharmacologic treatments of ADHD in improving outcomes associated with ADHD? How do these outcomes vary by presentation (inattentive, hyperactive/impulsive, and combined) or other comorbid conditions? What is the risk of diversion of pharmacologic treatment?

KQ 3: What are the comparative safety and effectiveness of different monitoring strategies to evaluate the effectiveness of treatment or changes in ADHD status (e.g., worsening or resolving symptoms)?

## **KQ 1: Diagnosis**

- **Population:**
  - Individuals through 17 years of age without the diagnosis of ADHD. This KQ will focus on the initial diagnosis. Subgroups of interest include the general population of children and adolescents: ages less than 4, 4-6, 7-12, and 13-17 years. Because of differences in the course of ADHD, findings will be separately evaluated by sex, race/ethnicity, socioeconomic status, insurance status, geographic location, or specific risk factors (prenatal tobacco, alcohol, or substance abuse; prematurity or low birth weight; and family history) when data are available. The influence of ADHD presentation and comorbidity will also be considered.
- **Interventions:**
  - Any standard ADHD diagnostic strategy, including clinician interview or standardized instrument (e.g., Vanderbilt scales, the Conner scales, and the SNAP-IV rating score). The use of EEG-based systems to support the diagnosis of ADHD will also be evaluated.
- **Comparators:**
  - The gold-standard comparator will be confirmation of diagnosis by a specialist, including psychologist or psychiatrist or other care provider using a well-validated and reliable process of confirming the diagnosis of ADHD according to the DSM-4 or DSM-5.
- **Outcomes:**
  - Accuracy of diagnostic strategy within primary care settings compared to assessment by specialty experts, as measured by diagnostic concordance. The specialists will be considered to be the “gold standard.” Primary care providers often use one or more standardized instruments and clinical judgment to determine whether a child fulfills the criteria for ADHD. This categorization may differ from the diagnostic classification provided by a specialist. We will also evaluate the internal consistency, test-retest, and inter-rater reliability of the included diagnostic strategies. When possible, the results of concordance between the diagnosis in the primary care setting and the diagnosis by the specialist will be converted into measures of sensitivity, specificity, positive predictive value, negative predictive value, false positives, false negatives, and risk of missed condition that can appear as ADHD (i.e., misdiagnosis) leading to incorrect treatment. Labeling will be any measure of stigma following diagnosis comparing those with and without ADHD. In order to fully understand stigma, parent and child attitudes toward the diagnosis of ADHD and the degree of stigma faced by the child related to the symptoms of ADHD will be assessed, when available.
- **Timing:**
  - To assess diagnostic accuracy, diagnostic follow-up must be within 4 months of the initial evaluation and must be completed before treatment is initiated. Timing for labeling can be any time after the ADHD diagnosis.

- **Settings:** Primary or specialty care settings

## KQ 2: Treatment

- **Population:**
  - Individuals through 17 years of age with a diagnosis of ADHD. Subgroups of interest include ages less than 4, 4-6, 7-12, and 13-17 years, with findings stratified by sex, ADHD presentation, comorbidity (e.g., anxiety, depression), and specific risk factor (as defined in KQ 1) when possible. We will also explore, when possible, subgroups defined by race/ethnicity, socioeconomic status, insurance status, or geographic location.
- **Interventions:** Any pharmacologic or nonpharmacologic treatment of ADHD, alone or in combination. Given that the potential range of treatment strategies for ADHD is broad and widely varied, and in consideration of time and resources, the final list of interventions analyzed will be determined in collaboration with an advisory panel of Technical Experts and the nominating partner as the review proceeds and more information is gathered regarding the availability of data and impact of included interventions on the size of the evidence base.
  - Pharmacologic treatments will include brand name and generic formulations of the following medications used in the management of ADHD:
    - Psychostimulants
      - Methylphenidate (MPH)
      - Dexmethylphenidate (D-TMP)
      - Dextroamphetamine (DEX)
      - Lisdexamfetamine (LDX)
      - Mixed amphetamine salts (MAS)
      - Amphetamine
    - Tricyclic antidepressants
      - Desipramine
      - Nortriptyline
    - Selective norepinephrine reuptake inhibitors
      - Atomoxetine (ATX)
    - Alpha-2 agonists
      - Clonidine
    - Guanfacine extended release (GXR) Dopamine reuptake inhibitors
      - Modafinil
      - Armodafinil
    - Norepinephrine-dopamine reuptake inhibitors
      - Bupropion
    - Serotonin-norepinephrine reuptake inhibitors
      - Duloxetine
    - Serotonin-norepinephrine-dopamine reuptake inhibitors
      - Venlafaxine
    - Monoamine oxidase type B inhibitors
      - Selegiline
    - N-methyl-D-aspartate receptor antagonists
      - Amantadine

- Memantine
  - Nonpharmacologic therapies include psychosocial interventions, behavioral interventions, cognitive behavioral therapy, play therapy, mindfulness-based therapies, school interventions, cognitive training therapies, biofeedback or neurofeedback, parent behavior training, dietary supplements (e.g., omega-3 fatty acids, vitamins, herbal supplements), homeopathy, acupuncture, elimination diets, vision training, exercise, and chiropractic treatment.
- **Comparators:** Specific treatments will be compared to other included treatments as described above or to no treatment.
- **Outcomes:**
  - Intermediate outcomes include changes on standardized symptom scores, progress toward patient-identified goals, and changes to functional impairment. Standardized symptom scores include narrow-band focused instruments (Vanderbilt rating scales, ADHD Rating Scale) and broad-band scales (Child Behavior Checklist and Teacher Report Form, Behavior Assessment System for Children, Conners' Rating Scales-Revised). Acceptability of treatment will also be evaluated as an intermediate outcome. The final outcomes to be considered include academic performance, workforce participation, quality of peer relationships, divorce/relationship status, motor vehicle collisions or other accidents, motor vehicle violations, risk-taking behaviors, incarceration or other interactions with the legal system (juvenile detention, probation, court-mandated interventions, need for residential placement), obesity, tobacco use, substance abuse, mood disorders, depression or anxiety, self-injurious nonsuicidal behavior, suicide (attempted or completed), suicidal ideation, and mortality.
  - Adverse effects of treatment include changes in appetite, growth suppression, weight decrease, sleep disturbance, gastrointestinal symptoms, elevated blood pressure, increased heart rate, risk of sudden cardiac death, cardiac arrhythmias, conduction abnormalities, tics or other movement disorders, behavior changes, hallucination, aggression, suicide (attempted or completed), suicidal ideation, overtreatment, diversion of pharmacotherapy, parental stress, personality change, time demands/opportunity cost, and loss of spontaneity. We will review FDA safety information about relevant ADHD medications (<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm283449.htm>) and ensure that our included adverse effects reflect listed potential risks.
- **Timing:** Any. Dose, duration, and fidelity to the treatment will be considered. Note that the duration of pharmacologic treatments or the fidelity to behavioral interventions will be assessed in the study's quality and applicability metrics.
- **Settings:** Any (primary care, specialty clinic, community resource). Findings will be stratified by setting.



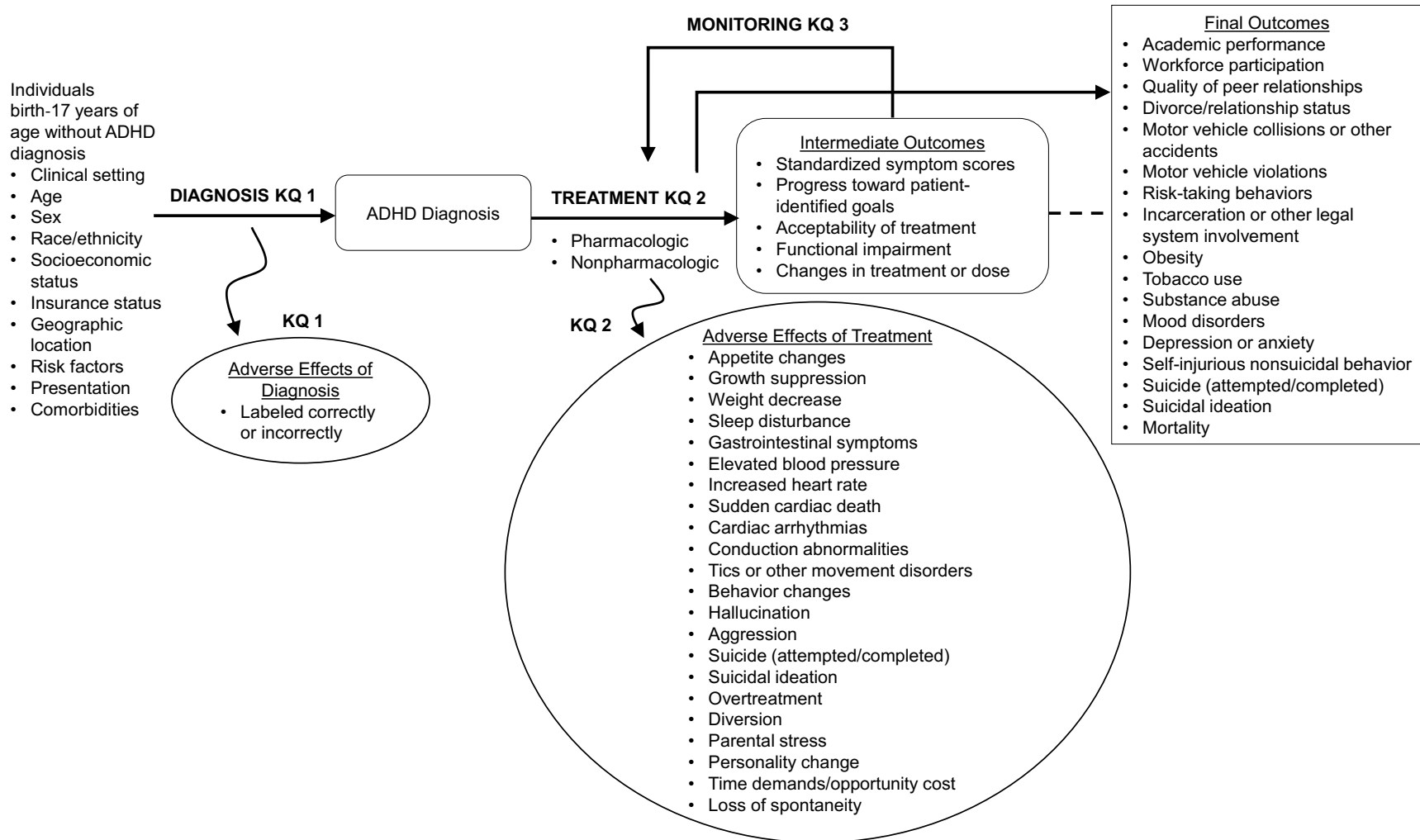
### **KQ 3: Frequency of follow-up and monitoring**

- **Population:**
  - Individuals through 17 years of age who have previously begun treatment for ADHD. Subgroups of interest include ages less than 4, 4-6, 7-12, and 13-17 years, with findings stratified by sex, ADHD presentation, comorbidity, and specific risk factor (as defined in KQ 1) when possible. We will also explore, when possible, subgroups defined by race/ethnicity, socioeconomic status, insurance status, or geographic location.
- **Interventions:**
  - Follow-up visits in primary care with various methods and within times (monthly to annually) for repeat monitoring, independent of treatment.
- **Comparators:** Follow-up will be compared to differing durations of follow-up or differing settings of follow-up.
- **Outcomes:**
  - Changes in treatment or dose, adverse effects of treatment, changes in intermediate outcomes (e.g., standardized symptom scores, progress toward patient-identified goals, functional impairment).
- **Timing:** Any, as above
- **Settings:** Any

### III. Analytic Framework

The analytic framework presented in Figure 1 illustrates the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis. This figure illustrates how individuals through 17 years of age without ADHD may be diagnosed and treated for ADHD, and how treatment is associated with a range of potential adverse effects and outcomes. Separate key questions were developed regarding the accuracy of diagnosis and the risk of misdiagnosis or labeling, the effectiveness and risk of adverse events associated with pharmacologic and/or nonpharmacologic treatments, and the need for reevaluation of ADHD symptoms over time.

**Figure 1. Analytic framework for ADHD**



## IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and evaluation of strength of evidence recommended by the Agency for Healthcare Research and Quality (AHRQ)'s EPC Program in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the Methods Guide).<sup>28</sup> We will solicit feedback regarding conduct of the work (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer and the Technical Expert Panel. We will follow the methodology recommended by the EPCs for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

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

**Table 1. Inclusion and exclusion criteria**

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	<p>KQ 1: Individuals birth through 17 years of age without the diagnosis of ADHD</p> <p>KQ 2: Individuals birth through 17 years of age with a diagnosis of ADHD</p> <p>KQ 3: Individuals birth through 17 years of age who have previously begun treatment for ADHD</p> <p>Subgroups of interest for KQs 1-3:</p> <ul style="list-style-type: none"> <li>• The general population of children and adolescents: ages less than 4, 4-6, 7-12, and 13-17 years</li> <li>• When data are available, findings will be separately evaluated by sex or specific risk factors (prenatal tobacco, alcohol, or substance abuse; prematurity or low birth weight; and family history); ADHD presentation; comorbidity; race/ethnicity; socioeconomic status; insurance status; geographic location</li> </ul>	<p>Individuals 18 years of age or older. Note that studies with individuals greater than 18 years of age will be included as long as findings are reported separately for individuals 18 years and under. Also note that for long-term studies, the age of the individuals may be greater than 18, but these studies will only be considered for inclusion if the age at enrollment in the study was 18 years or younger.</p>
Interventions	<p>KQ 1: Any standard ADHD diagnostic strategy, including clinician interview or standardized instrument (e.g., Vanderbilt scales, the Conner scales, and the SNAP-IV rating score). EEG-based systems will also be evaluated.</p> <p>KQ 2: Any pharmacologic or nonpharmacologic treatment of ADHD, alone or in combination:</p> <ul style="list-style-type: none"> <li>• Pharmacologic treatments include brand name and generic formulations of the following medications<sup>a</sup>: <ul style="list-style-type: none"> <li>○ Psychostimulants <ul style="list-style-type: none"> <li>▪ Methylphenidate (MPH)</li> <li>▪ Dexmethylphenidate (D-TMP)</li> <li>▪ Dextroamphetamine (DEX)</li> <li>▪ Lisdexamfetamine (LDX)</li> <li>▪ Mixed amphetamine salts (MAS)</li> <li>▪ Amphetamine</li> </ul> </li> <li>○ Tricyclic antidepressants <ul style="list-style-type: none"> <li>▪ *Desipramine</li> </ul> </li> </ul> </li> </ul>	<p>KQ 1: Validation studies or diagnosis conducted using a nonvalidated instrument</p>

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> <li>▪ *Nortriptyline</li> <li>○ Selective norepinephrine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ Atomoxetine (ATX)</li> </ul> </li> <li>○ Alpha-2 agonists <ul style="list-style-type: none"> <li>▪ Clonidine</li> <li>▪ Guanfacine extended release (GXR)</li> </ul> </li> <li>○ Dopamine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ *Modafinil</li> <li>▪ *Armodafinil</li> </ul> </li> <li>○ Norepinephrine-dopamine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ *Bupropion</li> </ul> </li> <li>○ Serotonin-norepinephrine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ *Duloxetine</li> </ul> </li> <li>○ Serotonin-norepinephrine-dopamine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ *Venlafaxine</li> </ul> </li> <li>○ Monoamine oxidase type B inhibitors <ul style="list-style-type: none"> <li>▪ *Selegiline</li> </ul> </li> <li>○ N-methyl-D-aspartate receptor antagonists <ul style="list-style-type: none"> <li>▪ *Amantadine</li> <li>▪ *Memantine</li> </ul> </li> <li>• Nonpharmacologic therapies include psychosocial interventions, behavioral interventions, cognitive behavioral therapy, play therapy, mindfulness-based therapies, school interventions, cognitive training therapies, biofeedback or neurofeedback, parent behavior training, dietary supplements (e.g., omega-3 fatty acids, vitamins, herbal supplements, probiotics), homeopathy, acupuncture, elimination diets, vision training, exercise, and chiropractic treatment.</li> </ul> <p>KQ 3: Follow-up visits in primary care with various methods and within times (monthly to annually) for repeat monitoring, independent of treatment.</p>	
Comparators	<p>KQ 1: Confirmation of diagnosis by a specialist (gold standard), including psychologist or psychiatrist or other care provider using a well-validated and reliable process of confirming the diagnosis of ADHD according to the DSM-4 or DSM-5.</p> <p>KQ 2: Specific treatments will be compared to other treatments as described above or to no treatment.</p> <p>KQ 3: Follow-up will be compared to differing durations of follow-up or differing settings of follow-up.</p>	KQ 1: Comparison to diagnosis with a nonvalidated instrument
Outcomes	<p>KQ 1:</p> <ul style="list-style-type: none"> <li>• Accuracy of diagnostic strategy, as measured by: <ul style="list-style-type: none"> <li>○ Diagnostic concordance of primary care provider with specialist</li> <li>○ Inter-rater reliability</li> <li>○ Internal consistency</li> <li>○ Test-retest</li> <li>○ Sensitivity</li> <li>○ Specificity</li> <li>○ Positive predictive value</li> <li>○ Negative predictive value</li> <li>○ False positives</li> <li>○ False negatives</li> <li>○ Risk of missed condition that can appear as ADHD (i.e., misdiagnosis)</li> </ul> </li> <li>• Labeling will be any measure of stigma following diagnosis</li> </ul>	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<p>comparing those with and without ADHD.</p> <p>KQ 2:</p> <ul style="list-style-type: none"> <li>• Intermediate outcomes: <ul style="list-style-type: none"> <li>○ Changes on standardized symptom scores or progress toward patient-identified goals. Standardized symptom scores include narrow-band focused instruments (Vanderbilt rating scales, ADHD Rating Scale) and broad-band scales (Child Behavior Checklist and Teacher Report Form, Behavior Assessment System for Children, Conners' Rating Scales-Revised)</li> <li>○ Acceptability of treatment</li> <li>○ Functional impairment</li> </ul> </li> <li>• Final outcomes include: <ul style="list-style-type: none"> <li>○ Academic performance</li> <li>○ Workforce participation</li> <li>○ Quality of peer relationships</li> <li>○ Divorce/relationship status</li> <li>○ Motor vehicle collisions or other accidents</li> <li>○ Motor vehicle violations</li> <li>○ Risk-taking behaviors</li> <li>○ Incarceration or other interactions with the legal system (juvenile detention, probation, court-mandated interventions, need for residential placement)</li> <li>○ Obesity</li> <li>○ Tobacco use</li> <li>○ Substance abuse</li> <li>○ Mood disorders</li> <li>○ Depression or anxiety</li> <li>○ Self-injurious nonsuicidal behavior</li> <li>○ Suicide (attempted or completed)</li> <li>○ Suicidal ideation</li> <li>○ Mortality</li> </ul> </li> <li>• Adverse effects of treatment, including: <ul style="list-style-type: none"> <li>○ Changes in appetite</li> <li>○ Growth suppression</li> <li>○ Weight decrease</li> <li>○ Sleep disturbance</li> <li>○ Gastrointestinal symptoms</li> <li>○ Elevated blood pressure</li> <li>○ Increased heart rate</li> <li>○ Risk of sudden cardiac death</li> <li>○ Cardiac arrhythmias</li> <li>○ Conduction abnormalities</li> <li>○ Tics or other movement disorders</li> <li>○ Behavior changes</li> <li>○ Hallucination</li> <li>○ Aggression</li> <li>○ Suicide (attempted or completed)</li> <li>○ Suicidal ideation</li> <li>○ Overtreatment</li> <li>○ Diversion of pharmacotherapy</li> <li>○ Parental stress</li> <li>○ Personality change</li> <li>○ Time demands/opportunity cost</li> <li>○ Loss of spontaneity</li> </ul> </li> </ul> <p>KQ 3:</p>	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> <li>• Changes in treatment or dose</li> <li>• Adverse effects of treatment as described under KQ 2</li> <li>• Changes in intermediate outcomes (e.g., standardized symptom scores, progress toward patient-identified goals, functional impairment) as described under KQ 2</li> </ul>	
Timing	KQ 1: <ul style="list-style-type: none"> <li>• For assessment of diagnostic accuracy: diagnostic follow-up must be within 4 months of the initial evaluation and must be completed before treatment is initiated</li> <li>• For labeling: any time after the ADHD diagnosis</li> </ul> KQs 2 and 3: Any	
Settings	KQ 1: Primary or specialty care settings KQs 2 and 3: Any	None
Study design	<ul style="list-style-type: none"> <li>• Original data</li> <li>• Randomized trials, prospective and retrospective observational studies with comparator; for diagnostic accuracy, cross-sectional studies are acceptable if they include patients with diagnostic uncertainty and direct comparison of diagnosis in primary care to diagnosis by a specialist</li> <li>• Randomized controlled trials: sample size <math>\geq 20</math> subjects</li> <li>• Observational studies: sample size <math>\geq 20</math> subjects</li> </ul>	Editorials, nonsystematic reviews, letters, case series, case reports, abstract-only  Because studies with fewer than 20 subjects are often pilot studies or studies of lower quality, we will exclude them from our review.
Publications	<ul style="list-style-type: none"> <li>• English-language only</li> <li>• Published January 1, 2009, to present</li> <li>• Relevant systematic reviews, meta-analyses, or methods articles (used for background only)</li> </ul>	Given the high volume of literature available in English-language publications, the focus of our review on applicability to populations in the United States, and the scope of our current KQs, non-English articles will be excluded. <sup>b</sup>

<sup>a</sup>Pharmacologic treatments listed are FDA-approved for an indication of ADHD with the exception of those marked with an asterisk, which are available within the United States and are FDA-approved but not specifically approved for ADHD.

<sup>b</sup>It is the opinion of the investigators that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ATX = atomoxetine; DEX = dextroamphetamine; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; D-TMP = dexamethylphenidate; EEG = electroencephalograph; GXR = guanfacine extended release; KQ = key question; LDX=lisdexamfetamine; MAS = mixed amphetamine salts; MPH = methylphenidate; PICOTS = Populations, Interventions, Comparators, Outcomes, Timing, Settings; RCT = randomized controlled trial

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

To identify relevant published literature, we will search PubMed<sup>®</sup>, Embase<sup>®</sup>, PsycINFO<sup>®</sup>, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies conducted in children 17 years of age and younger and published from January 1, 2009, to the present. These databases were selected based on internal expert opinion that they would identify most of the relevant literature on this topic and following prior related systematic reviews. We believe that the evidence published from 2009 both represents the current standard of care for the population of interest in this review and allows this report to build on the previous systematic review published in 2011 (and including literature through May 31, 2010).<sup>26</sup> Our proposed search strategy for PubMed is provided in Table 2; this strategy will be adapted as appropriate for searching the other databases. Where possible, we will use existing validated search filters (such as the Clinical Queries Filters in PubMed). An experienced search librarian will guide all searches. We will supplement the electronic searches with a manual search of citations from a set of key primary and review articles. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our database, and additional relevant manuscripts will be retrieved. All citations will be imported into an electronic bibliographical database (EndNote<sup>®</sup> Version X7; Thomson Reuters, Philadelphia, PA).

**Table 2. PubMed search strategy for ADHD**

### KQ 1 Diagnosis:

Set #	Terms
#1	"Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR "ADHD"[tiab] OR "attention deficit disorder"[tiab]
#2	"Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR infant[tiab] OR infants[tiab] OR preschool[tiab] OR preschooler[tiab] OR pediatric[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR youth[tiab]
#3	"Attention Deficit and Disruptive Behavior Disorders/diagnosis"[Majr] OR mass screening[mesh] OR questionnaires[mesh] OR Interviews as Topic[Mesh] OR Psychometrics[Mesh] OR Psychiatric Status Rating Scales[Mesh] OR diagnosis[mesh:noexp] OR "Diagnostic Techniques and Procedures"[Mesh] OR "Diagnostic and Statistical Manual of Mental Disorders"[Mesh] OR "Referral and Consultation"[Mesh] OR questionnaire[tiab] OR questionnaires[tiab] OR screening[tiab] OR screen[tiab] OR scale[tiab] OR instrument[tiab] OR instruments[tiab] OR interview[tiab] OR interviews[tiab] OR DSM*[tiab] OR diagnosis[tiab] OR diagnostic[tiab] OR diagnosed[tiab] OR (Vanderbilt[tiab] AND scale[tiab]) OR conners[tiab] OR cprs[tiab] OR ctrs[tiab] OR cprs[tiab] OR crs[tiab] OR "snap-IV"[tiab] OR "snap-4"[tiab] OR "basc-2"[tiab] OR "behavioral assessment system for children"[tiab] OR dbdrs[tiab] OR "disruptive behavior disorder rating scale"[tiab] OR adhd-rs[tiab] OR "adhd rating scale"[tiab] OR ksads[tiab] OR k-sads[tiab] OR kiddie-sads[tiab] OR DISC[tiab] OR "dominance inducement submission and compliance"[tiab] OR "diagnostic interview schedule for children"[tiab] OR "diagnostic inventory for screening children"[tiab] OR "mini-kid"[tiab] OR "Mini Interational Neuropsychiatric interview"[tiab] OR "iva-2"[tiab] OR "iva-qs"[tiab] OR "iva-ae2"[tiab] OR tova[tiab] OR "test of variables of attention"[tiab] OR "neuropsychiatric eeg-based assessment aid"[tiab] OR neba[tiab]
#4	"Sensitivity and Specificity"[Mesh] OR "Diagnostic Errors"[Mesh] OR sensitivity[tiab] OR specificity[tiab] OR accuracy[tiab] OR accurate[tiab] OR accurately[tiab] OR misdiagnos*[tiab] OR (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[pt] OR "evaluation studies as topic"[MeSH] OR "evaluation

Set #	Terms
	study[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH] OR "case-control"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH] OR "retrospective"[tiab] OR "Cross-Sectional Studies"[Mesh] OR cross-sectional[tiab] OR "comparative study"[pt] OR "comparative study"[tiab] OR systematic[sb] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] NOT (Editorial[ptyp] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) NOT (animals[mh] NOT humans[mh]) AND English[la]
#5	#1 AND #2 AND #3 AND #4
#6	#5, since 2009

### KQ 2 Treatment:

Set #	Terms
#1	"Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR ADHD[tiab] OR "attention deficit disorder"[tiab]
#2	"Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR infant[tiab] OR infants[tiab] OR preschool[tiab] OR preschooler[tiab] OR pediatric[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR youth[tiab]
#3	#1 AND #2
#4	"Attention Deficit Disorder with Hyperactivity/drug therapy"[Majr] OR "Central Nervous System Stimulants"[MeSH] OR "Methylphenidate"[MeSH] OR "Dexamethylphenidate"[MeSH] OR "Dextroamphetamine"[MeSH] OR "Adderall"[Supplementary Concept] OR "lisdexamfetamine dimesylate"[Supplementary Concept] OR "Amphetamine"[MeSH] OR "Guanfacine"[MeSH] OR "Sympatholytics"[MeSH] OR "Clonidine"[MeSH] OR "Adrenergic Uptake Inhibitors"[MeSH] OR "Adrenergic Uptake Inhibitors"[Pharmacological Action] OR "Receptors, Adrenergic, alpha-2"[MeSH] OR "Adrenergic alpha-Agonists"[Mesh] OR "Adrenergic alpha-2 Receptor Agonists"[Mesh] OR "atomoxetine"[Supplementary Concept] OR "Antidepressive Agents, Tricyclic"[MeSH] OR "Desipramine"[MeSH] OR "Dopamine Uptake Inhibitors"[MeSH] OR "Sympathomimetics"[MeSH] OR "modafinil"[Supplementary Concept] OR "Serotonin Uptake Inhibitors"[MeSH] OR "Serotonin Uptake Inhibitors"[Pharmacological Action] OR "duloxetine"[Supplementary Concept] OR "Monoamine Oxidase Inhibitors"[MeSH] OR "Monoamine Oxidase"[MeSH] OR "Selegiline"[MeSH] OR "Bupropion"[MeSH] OR "armodafinil"[Supplementary Concept] OR "venlafaxine"[Supplementary Concept] OR "Receptors, N-Methyl-D-Aspartate"[MeSH] OR "Memantine"[MeSH] OR "Amantadine"[MeSH] OR "duloxetine"[Supplementary Concept] OR "Central Nervous System Stimulants" [Pharmacological Action] OR "Adrenergic alpha-2 Receptor Agonists" [Pharmacological Action] OR "Antidepressive Agents, Tricyclic" [Pharmacological Action] OR "Dopamine Uptake Inhibitors" [Pharmacological Action] OR "Monoamine Oxidase Inhibitors" [Pharmacological Action] OR "Central Nervous System Stimulants"[tiab] OR "psychostimulant"[tiab] OR "Methylphenidate"[tiab] OR "Methylphenidate Hydrochloride"[tiab] OR "Aptensio"[tiab] OR "Concerta"[tiab] OR "Ritalin"[tiab] OR "Ritalin LA"[tiab] OR "Medikinet"[tiab] OR "Equasym"[tiab] OR "Quillivant"[tiab] OR "Metadate"[tiab] OR "Daytrana"[tiab] OR "Dexamethylphenidate"[tiab] OR "Dexamethylphenidate Hydrochloride"[tiab] OR "Focalin"[tiab] OR "Dextroamphetamine"[tiab] OR "Dexedrine"[tiab] OR "Dextrostat"[tiab] OR "ProCentra"[tiab] OR "Zenedi"[tiab] OR "mixed amphetamine salts"[tiab] OR "Adderall" [tiab] OR "lisdexamfetamine"[tiab] OR "lisdexamfetamine dimesylate"[tiab] OR "Vyvanse"[tiab] OR "Venvanse"[tiab] OR "Elvanse"[tiab] OR "Tyvense"[tiab] OR "Dyanavel"[tiab] OR "Evekeo"[tiab] OR "Guanfacine"[tiab] OR "Sympatholytics"[tiab] OR "Central alpha-2 Adrenergic Agonist"[tiab] OR "Clonidine"[tiab] OR "Intuniv"[tiab] OR "Estulic"[tiab] OR "Tenex"[tiab] OR "Catapres"[tiab] OR "Clophelin"[tiab] OR "Kapvay"[tiab] OR "Nexiclon"[tiab] OR "Duraclon"[tiab] OR "Norepinephrine Reuptake Inhibitors"[tiab] OR "Selective Norepinephrine Reuptake Inhibitors"[tiab] OR "Adrenergic Uptake Inhibitors"[tiab] OR "atomoxetine"[tiab] OR "Strattera"[tiab] OR "Tricyclic antidepressants"[tiab] OR "Desipramine"[tiab] OR "Norpramin"[tiab] OR "Nortriptyline"[tiab] OR "Pamelor"[tiab] OR "Dopamine Reuptake Inhibitors"[tiab] OR



Set #	Terms
	"modafinil"[tiab] OR "Provigil"[tiab] OR "Armodafinil"[tiab] OR "Norepinephrine-dopamine Reuptake Inhibitors"[tiab] OR "Bupropion"[tiab] OR "Wellbutrin"[tiab] OR "Forfivo"[tiab] OR "Cymbalta"[tiab] OR "venlafaxine"[tiab] OR "reboxetine"[tiab] OR "Monoamine Oxidase Type B inhibitors"[tiab] OR "Selegiline"[tiab] OR "Eldepryl"[tiab] OR "Zelapar"[tiab] OR "NMDA receptors"[tiab] OR "N-Methyl-D-aspartate receptor Antagonists"[tiab] OR "Amantadine"[tiab] OR "Memantine"[tiab] OR "Pertofrane"[tiab] OR "Nuvigil"[tiab] OR "Cymbalta"[tiab] OR "duloxetine"[tiab] OR "Effexor"[tiab] OR "Eldepryl"[tiab] OR "Emsam"[tiab] OR "Trevilor"[tiab] OR "Symmetrel"[tiab] OR "Namenda"[tiab] OR "Zelapar"[tiab]
<b>#5</b>	"Attention Deficit Disorder with Hyperactivity/diet therapy"[Majr] OR "Attention Deficit Disorder with Hyperactivity/rehabilitation"[Majr] OR "Psychotherapy"[MeSH] OR "Behavior Therapy"[MeSH] OR "Parent-Child Relations"[MeSH] OR "Play Therapy"[MeSH] OR "Cognitive Therapy"[MeSH] OR "Time Management"[MeSH] OR "Biofeedback, Psychological"[MeSH] OR "Neurofeedback"[MeSH] OR "Computer-Assisted Instruction"[MeSH] OR "Feedback, Psychological"[MeSH] OR "Diet Therapy"[MeSH] OR "Fatty Acids, Omega-3/therapeutic use"[MeSH] OR "Vitamins/administration and dosage"[MeSH] OR "Vitamins/therapeutic use"[MeSH] OR "Food Additives/adverse effects"[MeSH] OR "Probiotics/therapeutic use"[MeSH] OR "Acupuncture Therapy"[MeSH] OR "Remedial Teaching"[MeSH] OR "Early Intervention (Education)"[MeSH] OR "Complementary Therapies"[MeSH] OR "Combined Modality Therapy"[MeSH] OR "psychosocial therapy"[tiab] OR "psychosocial intervention"[tiab] OR "psychosocial interventions"[tiab] OR "psychosocial approach"[tiab] OR "psychosocial approaches"[tiab] OR "psychosocial treatment"[tiab] OR "psychosocial support"[tiab] OR "psychoeducation"[tiab] OR "nonpharmacologic therapy"[tiab] OR "nondrug therapy"[tiab] OR "non-drug therapy"[tiab] OR "Play Therapy"[tiab] OR "cognitive behavioral therapy"[tiab] OR "cognitive behavior therapy"[tiab] OR "cognitive behavioural therapy"[tiab] OR "cognitive behaviour therapy"[tiab] OR Mindfulness[tiab] OR complementary[tiab] OR "alternative medicine"[tiab] OR "alternative therapy"[tiab] OR "alternative therapies"[tiab] OR "Interpersonal skills training"[tiab] OR "Parent-Child Interaction Therapy"[tiab] OR "parent training"[tiab] OR "parent engagement"[tiab] OR "parent management"[tiab] OR "parenting skills"[tiab] OR "parenting intervention"[tiab] OR "parenting interventions"[tiab] OR "Barkley's defiant child"[tiab] OR "Teacher-Child Interaction Training"[tiab] OR "Incredible Years"[tiab] OR "New Forest Parenting"[tiab] OR "Triple P"[tiab] OR "Helping the Noncompliant Child"[tiab] OR "child life and attention skills"[tiab] OR "clas"[tiab] OR PCIT[tiab] OR "parent child interaction therapy"[tiab] OR "Summer Treatment Program"[tiab] OR "Daily Report Card"[tiab] OR "organization skills"[tiab] OR "organizational skills"[tiab] OR "time management"[tiab] OR "homework intervention"[tiab] OR braintrain[tiab] OR "memory training"[tiab] OR "Captain's log mindpower builder"[tiab] OR "memory gyms"[tiab] OR "attention gym"[tiab] OR "smartdriver plus"[tiab] OR "smartmind pro"[tiab] OR "RoboMemo"[tiab] OR "play attention"[tiab] OR metronome[tiab] OR brainmaster[tiab] OR mindmed[tiab] OR "attention lab"[tiab] OR (activate[tiab] AND c8[tiab]) OR "attention training"[tiab] OR "CogniPlus"[tiab] OR cogmed[tiab] OR "working memory training"[tiab] OR biofeedback[tiab] OR neurofeedback[tiab] OR neuroagility[tiab] OR neurooptimal[tiab] OR acupuncture[tiab] OR "vision training"[tiab] OR "visual training"[tiab] OR "vision therapy"[tiab] OR "education intervention"[tiab] OR "cognitive remediation"[tiab] OR neurotherapy[tiab] OR "elimination diet"[tiab] OR "diet therapy"[tiab] OR ("low carb" OR "low carbohydrate" OR "low carbohydrates"[tiab] OR "gluten free") AND diet[tiab] OR "feingold diet"[tiab] OR "red dye"[tiab] OR ((vitamin[tiab] OR vitamins[tiab]) AND (supplement[tiab] OR supplements[tiab])) OR "herbal supplement"[tiab] OR "herbal supplements"[tiab] OR probiotics[tiab] OR "omega 3"[tiab] OR "slow cortical potentials"[tiab] OR "few foods diet"[tiab] OR "oligoantigenic diet"[tiab] OR "restriction diet"[tiab] OR "food intolerance"[tiab] OR "food allergy"[tiab] OR "food allergies"[tiab] OR "food sensitivity"[tiab] OR "food sensitivities"[tiab] OR "multimodal treatment"[tiab] OR homeopathy[tiab] OR homeopathic[tiab] OR chiropractic[tiab] OR chiropractor[tiab]
<b>6</b>	#4 OR #5
<b>7</b>	#3 AND #6

Set #	Terms
8	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[pt] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention studies"[MeSH] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH] OR "case-control"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective"[tiab] OR "comparative study"[pt] OR "comparative study"[tiab] OR systematic[sb] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) NOT (animals[mh] NOT humans[mh]) AND English[la]
9	#7 AND #8
10	#9, since 2009

### KQ 3 Frequency of follow-up and monitoring:

Set #	Terms
#1	"Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR ADHD[tiab] OR "attention deficit disorder"[tiab]
#2	"Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR infant[tiab] OR infants[tiab] OR preschool[tiab] OR preschooler[tiab] OR pediatric[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR youth[tiab]
#3	"Secondary Care"[Mesh] OR "Comprehensive Health Care"[Mesh] OR "primary care"[tiab] OR monitor[tiab] OR monitored[tiab] OR monitoring[tiab] OR "follow up"[tiab] OR "followed up"[tiab] OR visit[tiab] OR visits[tiab] OR session[tiab] OR sessions[tiab] OR appointment[tiab] OR appointments[tiab]
#4	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[pt] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention studies"[MeSH] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH] OR "case-control"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective"[tiab] OR "comparative study"[pt] OR "comparative study"[tiab] OR systematic[sb] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) NOT (animals[mh] NOT humans[mh]) AND English[la]
#5	#1 AND #2 AND #3 AND #4
#6	#5, since 2009

As a mechanism to ascertain publication bias in recent studies, we will search ClinicalTrials.gov to identify completed but unpublished studies (we will also explore the possibility of publication bias specifically in our quantitative synthesis of the included literature through meta-analysis techniques). While the draft report is under peer review, we will update the search and include any eligible studies identified either during that search or through peer or public reviews in the final report.

We will use several approaches to identifying relevant gray literature, including requests to drug and device manufacturers for scientific information packets and a search of U.S. Food and Drug Administration (FDA) device registration studies and new drug applications. We will also review the known adverse effects of ADHD medications monitored by the FDA (<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm283449.htm>) and include in our outcomes list new potential adverse effects reported by the FDA. We will also search study registries for relevant articles from completed studies. Gray literature databases will include ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal, and the National Guidelines Clearinghouse.

For citations retrieved from MEDLINE, Embase, PsycINFO, and the CDSR, two reviewers using prespecified inclusion/exclusion criteria will review titles and abstracts for potential relevance to the research questions. Inclusion at the title screening level will be liberal; if a single reviewer believes an article may contain relevant information based on title, the article will move to the next level (abstract) for further screening. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision. Disagreements that cannot be resolved by the two reviewers will be resolved by a third expert member of the team. Articles meeting eligibility criteria (see Table 1) will be included for data abstraction. At random intervals during screening, quality checks by senior team members will occur to ensure that screening and abstraction is consistent with inclusion/exclusion criteria and abstraction guidelines. We will make screening decisions and abstract data based on the published literature and available online appendices. We will not contact study authors for additional data. All results will be tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

#### Data Abstraction and Data Management

The research team will create data abstraction forms for the KQs that will be programmed in the DistillerSR software. Based on their clinical and methodological expertise, a pair of researchers will be assigned to abstract data from each of the eligible articles. One researcher will abstract the data, and the second will over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached. We will link studies to avoid duplication of patient cohorts. Guidance documents will be drafted and provided to the researchers to aid both reproducibility and standardization of data collection.

We will design the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events

outcomes). We will pay particular attention to describing the details of the treatment (e.g., pharmacotherapy dosing, methods of behavioral interventions), patient characteristics (e.g., ADHD presentation, comorbidities, age), and study design (e.g., RCT versus observational) that may be related to outcomes. In addition, we will describe comparators carefully, as treatment standards may have changed during the period covered by the review. The safety outcomes will be framed to help identify adverse events, including those from drug therapies and those resulting from misdiagnosis and labeling. Data necessary for assessing quality and applicability, as described in the Methods Guide,<sup>28</sup> will also be abstracted. Before they are used, abstraction form templates will be pilot-tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency and reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles. Final abstracted data will be uploaded to SRDR per EPC requirements.

### Assessment of Methodological Risk of Bias of Individual Studies

We will assess methodological quality, or risk of bias, for each individual study based on the Cochrane Risk of Bias<sup>29</sup> tool for randomized studies, and the Newcastle-Ottawa Scale<sup>30</sup> for observational studies. We will supplement these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the AHRQ's Methods Guide.<sup>28</sup> Briefly, we will rate each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies. For all studies, the overall study quality will be assessed as follows:

- Good (low risk of bias). These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- Fair. These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- Poor (high risk of bias). These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

The grading will be outcome-specific such that a given study that analyzes its primary outcome well but did an incomplete analysis of a secondary outcome would be assigned a different quality grade for each of the two outcomes. Studies of different designs will be graded within the context of their respective designs. Thus, RCTs will be graded good, fair, or poor, and observational studies will separately be graded good, fair, or poor.

## Data Synthesis

We will begin by summarizing key features of the included studies for each KQ. To the degree that data are available, we will abstract information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes. We will order our findings by treatment or diagnostic comparison and then within these comparisons by outcome with long-term final outcomes emphasized.

We will review and highlight studies using a hierarchy-of-evidence approach. The best evidence available will be the focus of our synthesis for each key question. If high quality evidence is not available we will describe any lower quality evidence we were able to identify, but we will underscore the issues that make it lower quality and the uncertainties in our findings. We will assess and state whether the inclusion of lower quality studies would change any of our conclusions and perform sensitivity analyses excluding this evidence where appropriate.

We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature (we will require 3 appropriate studies to consider meta-analysis), conceptual homogeneity of the studies, and completeness of the reporting of results. When a meta-analysis is appropriate, we will use random-effects models to synthesize the available evidence quantitatively. We will test for heterogeneity using graphical displays and test statistics (Q and I<sup>2</sup> statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. We will present summary estimates, standard errors, and confidence intervals. We anticipate that intervention effects may be heterogeneous. We hypothesize that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation will be associated with the intervention effects. If there are sufficient studies, we will perform subgroup analyses and/or meta-regression analyses to examine these hypotheses. We will perform quantitative and qualitative syntheses separately by study type and discuss their consistency qualitatively.

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

We will grade the strength of evidence for each outcome assessed; thus, the strength of evidence for two separate outcomes in a given study may be graded differently. The strength of evidence will be assessed using the approach described in AHRQ's Methods Guide.<sup>28</sup> In brief, the approach requires assessment of five domains: study limitations (previously named risk of bias), consistency, directness, precision, and reporting bias, which includes publication bias, outcome reporting, and analysis reporting bias. Additional domains to be used when appropriate (most relevant to observational studies) are coherence, dose-response association, impact of plausible residual confounders, and strength of association (magnitude of effect). These domains will be considered qualitatively, and a summary rating of high, moderate, or low strength of evidence will be assigned for each outcome after discussion by two reviewers. In some cases, high, moderate, or low ratings will be impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" will be assigned. This four-level rating scale consists of the following definitions:

- 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.

### Assessing Applicability

We will assess applicability across our key questions using the method described in AHRQ’s Methods Guide.<sup>28</sup> In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, ADHD presentations, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control group) rates of events, intervention group rates of events, or both. We will use a checklist to guide the assessment of applicability. We will use these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, the possibility of diagnostic tool or treatment intervention learning curves, and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

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## VI. Definition of Terms

ADHD	Attention-deficit/hyperactivity disorder
ATX	Atomoxetine
DEX	Dextroamphetamine
DSM-4	<i>Diagnostic and Statistical Manual of Mental Disorders</i> , 4 <sup>th</sup> Edition
DSM-5	<i>Diagnostic and Statistical Manual of Mental Disorders</i> , 5 <sup>th</sup> Edition
D-TMP	Dexamethylphenidate
EEG	Electroencephalograph
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GXR	Guanfacine extended release
KQ	Key question
LDX	Lisdexamfetamine
MAS	Mixed amphetamine salts
MPH	Methylphenidate
PICOTS	Population, interventions, comparators, outcomes, timing, settings
RCT	Randomized controlled trial

## VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol.

Date	Section	Original Protocol	Revised Protocol	Rationale
6/9/2016	Section II. The Key Questions	<p>KQ 1: What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals through 17 years of age?</p> <p>a. How does the comparative diagnostic accuracy of these approaches vary by clinical setting, including primary care or specialty clinic, or patient subgroup, including age, sex, or other risk factors associated with ADHD?</p> <p>b. What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD?</p>	<p>KQ 1: For the diagnosis of ADHD:</p> <p>a. What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals younger than 7 years of age?</p> <p>b. What is the comparative diagnostic accuracy of EEG, imaging, or executive function approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals age 7 through 17 years of age?</p> <p>c. For both populations, how does the comparative diagnostic accuracy of these approaches vary by clinical setting, including primary care or specialty clinic, or patient subgroup, including age, sex, or other risk factors associated with ADHD?</p> <p>d. What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD?</p>	<p>This change documents a revision of KQ 1 performed in consultation with the nominating partner and the TEP in order to focus the question on the areas of the greatest uncertainty and potential impact. These revisions were defined prior to seeing the results of any studies and were determined to be the best approach to narrow the scope after finding the number of studies (but not results) while limiting any potential bias.</p>
6/9/2016	Section II. The Key Questions	<p>KQ 1 Population: Individuals through 17 years of age without the diagnosis of ADHD. This KQ will focus on the initial diagnosis.</p>	<p>KQ 1 Population: Individuals through 17 years of age without the diagnosis of ADHD, divided by subquestion as follows:</p> <ul style="list-style-type: none"> <li>• KQ 1a will consider the initial diagnosis of individuals under 7 years of age.</li> <li>• KQ 1b will consider the initial diagnosis of individuals through 17 years of age through EEG, imaging, or executive function approaches.</li> <li>• KQs 1c-d will consider both populations.</li> </ul>	<p>Revision of the KQ 1 Population portion of the PICOTS to reflect the revised KQ.</p>

6/9/2016	Section II. The Key Questions  Section IV, Table 1	<p>KQ 1 Interventions: Any standard ADHD diagnostic strategy, including clinician interview or standardized instrument (e.g., Vanderbilt scales, the Conner scales, and the SNAP-IV rating score). The use of EEG-based systems to support the diagnosis of ADHD will also be evaluated.</p> <p>Similar language was used in Table 1.</p>	<p>KQ 1 Interventions: Any standard ADHD diagnostic strategy, including clinician interview or standardized instrument (e.g., Vanderbilt scales, the Conner scales, and the SNAP-IV rating score) for individuals under 7 years of age. The use of EEG-based systems, imaging, or executive function approaches will be evaluated in the diagnosis of ADHD in individuals through 17 years of age.</p> <p>Language in Table 1 was similarly revised.</p>	Revision of the KQ 1 Interventions portion of the PICOTS to reflect the revised KQ.
6/9/2016	Section II. The Key Questions	<p>KQ 2 Interventions: Any pharmacologic or nonpharmacologic treatment of ADHD, alone or in combination. Given that the potential range of treatment strategies for ADHD is broad and widely varied, and in consideration of time and resources, the final list of interventions analyzed will be determined in collaboration with an advisory panel of Technical Experts and the nominating partner as the review proceeds and more information is gathered regarding the availability of data and impact of included interventions on the size of the evidence base.</p>	<p>KQ 2 Interventions: Given that the potential range of treatment strategies for ADHD is broad and widely varied, and in consideration of time and resources, the final list of interventions analyzed will be determined in collaboration with an advisory panel of Technical Experts and the nominating partner as the review proceeds and more information is gathered regarding the availability of data and impact of included interventions on the size of the evidence base. Due to the large amount of evidence available, we will require studies comparing two or more pharmacologic treatments approved by the FDA for the treatment of ADHD to include 100 or more patients with ADHD and have a follow-up period of 6 months or longer. Criteria will be less stringent for studies assessing nonpharmacologic treatments or pharmacologic treatments not indicated by the FDA for the treatment of ADHD. Data for these interventions will be</p>	This change documents a revision of KQ 2 scope performed in consultation with the nominating partner and the TEP in order to focus the question on the areas of the greatest uncertainty and potential impact. These revisions were defined prior to seeing the results of any studies and were determined to be the best approach to narrow the scope after finding the number of studies (but not results) while limiting any potential bias.

			limited to studies including 50 or more patients with ADHD, with no specific requirement for length of follow-up.	
6/9/2016	Section II. The Key Questions  Section IV, Table 1 - Interventions	The KQ 2 interventions lists were prefaced with a statement “will include.”  Similar language was used in Table 1	The preface language for these lists was clarified to “pharmacologic treatments considered” and “nopharmacologic therapies considered.”  Language in Table 1 was similarly revised.	Refinement of the language to provide more clarity on the interventions of interest
6/9/2016	Section IV, Table 1 - Interventions		Item added to the Exclusion Criteria column of the Interventions row:  KQ2: Studies comparing pharmacologic agents approved by the FDA for the treatment of ADHD that have enrollment of fewer than 100 patients with ADHD, or less than 6 months of follow-up	Criterion added to reflect the change in KQ2 scope discussed above.
6/9/2016	Section IV, Table 1 – Study design	Specified exclusion of studies including fewer than 20 subjects for all KQs	For KQ 2, added exclusion of studies with fewer than 50 subjects with ADHD (or 100 subjects for studies comparing two or more pharmacological treatments approved by the FDA for the treatment of ADHD)	Criterion added to reflect the change in KQ2 scope discussed above.
6/9/2016	Section IV, Table 1 – Study design		Added pre-post studies to the Exclusion Criteria column’s list of excluded study designs	Added for explicit clarity on exclusion of pre-post studies. All studies must have a comparator.
6/9/2016	Section IV. Methods, Searching the Evidence		Added to the language describing scientific information packets to note that the information was solicited through the AHRQ Effective Health Care website and a notice posted in the Federal Register.	Clarified the AHRQ process for requesting scientific information packets.

6/9/2016	Section IV. Methods, Searching the Evidence	Original protocol anticipated a search of FDA device registration studies and new drug applications (NDAs) as part of the gray literature assessment	Search of this source no longer proposed; gray literature assessment will include ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal, and the National Guidelines Clearinghouse.	In the opinion of the investigators, the FDA source was determined unlikely to provide additional impactful data beyond that available in the literature to be searched.
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### VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

### IX. Key Informants

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

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

## X. Technical Experts

Technical Experts constitute a multidisciplinary 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.

## XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

## XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

### XIII. Role of the Funder

This project was funded under Contract No. HHS A290201500004I 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.