Evidence-based Practice Center Systematic Review Protocol

Project Title: Anxiety in Children

I. Background and Objectives for the Systematic Review

Childhood anxiety disorders are very common, affecting one in eight children[1]. The National Institute of Mental Health (NIMH) estimates a lifetime prevalence between the ages 13 and 18 years of 25.1% and a lifetime prevalence of 5.9% for "severe" anxiety disorder[2]. Anxiety disorders in childhood generally follow an unremitting course leading to additional psychopathology and often interfere with social, emotional, and academic development[3, 4]. Early intervention is especially important given the childhood onset and unrelenting course of anxiety disorders.

Multiple treatment options are available, including psychotherapy, pharmacotherapy, and combined treatment approaches. Cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitor (SSRI's) are considered by many to be first line treatments[5-9]. CBT is generally recommended as the first-line treatment by World Health Organization (WHO), National Institute for Health and Care Excellence (NICE), and British Columbia Medical Services Commission[10-12]. In addition to CBT, other psychotherapy approaches include: psychoanalysis, family therapy, and education support. Pharmacotherapy is also widely used, including selective reuptake inhibitor (SRI), serotonin–norepinephrine reuptake inhibitor (SNRI), benzodiazepines, and others. Pharmacotherapy is commonly used when psychotherapy is not available, does not lead to adequate response, or for moderate or severe symptoms at initial presentation.

There is a great deal of uncertainty regarding comparative effectiveness and safety of all treatments for childhood anxiety disorders. The potential advantage of psychotherapy is related to being safe and noninvasive[5, 6]. The potential disadvantages are that it has limited availability[13], requires multiple appointments[14], and requires behavioral changes by children and families. The potential disadvantages of pharmacotherapy are that it has unknown effect on brain chemistry, has the potential for adverse events[15, 16], and that its benefits may not persist after treatment has been discontinued[17, 18]. Currently, existing treatment guidelines provide inconsistent and at times conflicting advice[10, 11, 19]. Regarding SRIs, one guideline specifically recommends that SRIs should not be used in children[11], while another recommends they be used if CBT is not sufficient[10], and the third recommends their use for more severe presentations or if CBT is not available[19]. Furthermore, despite the fact that all guidelines recommended CBT as a first line treatment, the components that comprise CBT differ between guidelines. In addition, one guideline suggested mild severity be treated with general health promotion[10], another recommended CBT regardless of severity[11], and the third recommended CBT as a sole intervention only for mild to moderate symptoms[19]. Regarding other behavioral interventions, one organization specifically recommended that they should not be used[11], another did not comment[10], and the third recommended that multiple different interventions be considered including modalities that were later in the guidelines described as having little to no empirical support[19]. In addition, there were inconsistency between several recommendations and the supporting data, particularly when discussing

the role of symptom severity in treatment decisions, the comparative effectiveness of different SRIs, the use of SRIs in preschool age youth, and the use of non-SRIs medications[20-22]. Finally, additional inconsistencies exists between guidelines, such as the level of empirical support ascribed to an intervention, the relative value of different treatment modalities, or the classification of a treatment protocol.

Based on the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), we plan to study the following types of anxiety: panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder, and separation anxiety. Obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) will be excluded as their treatment approaches are generally different from other types of anxiety.

While various scales are used to evaluate the symptoms of anxiety in children, we plan to focus on patient-centered outcomes, including remission, anxiety symptoms, behavioral problems, parent distress, therapeutic alliance, school attendance, reduction in impairment, quality of life and avoiding hospitalization. Therefore, we will include studies that reported such patient centered outcomes measured with scales that are widely available and validated; which are:(patients/parent reported and clinician assessed), including the Screen for Anxiety-Related Emotional Disorders (SCARED), the Revised Children's Manifest Anxiety Scale (RCMAS), the Beck Anxiety Inventory, the Multidimensional Anxiety Scale for Children (MASC), the Liebowitz Social Anxiety Scale, and the Social Phobia and Anxiety Inventory for Children, Spence Children's Anxiety Scale (child and parent report (SCAS); Fear Survey Schedule for Children – Revised; State-Trait Anxiety Inventory- Child (STAIC); and Anxiety Disorder Interview Schedule-Child Version.

Many factors have been proposed to interfere with participation or adherence to treatment and/or response to treatments, including severity of illness, comorbid conditions, family socioeconomic status (SES), externalizing symptoms, patient age, and others. For example, treatment for children under six usually involves primarily parent training/behavior management interventions; while treatment with children 6 and up is more likely to involve working directly with children. Evidence reviews and randomized controlled trials (RCTs) reported conflicting results regarding differential response rates by age groups[23]. Severity of symptoms are generally believed to associated with worse outcomes and guidelines suggest a different treatment approach for these children[11, 19]. Despite many available treatments, the majority of children with anxiety disorders do not receive treatment[24].

The objectives of this systematic review are: 1) to evaluate the comparative effectiveness of psychotherapy and pharmacotherapy for childhood anxiety disorders, including panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder, and separation anxiety, and 2) to evaluate the harms and safety concerns associated with those treatments.

II. The Key Questions

During Topic Refinement, we developed the Key Questions (KQs) with inputs from Key Informants, American Psychological Association (APA), and American Academy of Child & Adolescent Psychiatry (AACAP). The drafted KQs were posted for public

comment from April 28, 2016 to May 18, 2016. Public comments led to the inclusion of additional subgroups of interest; the inclusion of problem solving therapy (PST) and interpersonal psychotherapy (IPT) as additional treatment modalities, and clarification of comorbidities and other potential effect modifiers. There were no other significant changes.

The following are the KQs to be studied by the review:

KQ1: What is the comparative effectiveness of the available treatments for childhood anxiety disorders, including panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder, and separation anxiety?

    a. What is the evidence for the comparative effectiveness of psychotherapy, pharmacotherapy, and combined treatment approaches for childhood anxiety disorders?

    b. What is the evidence of differential effectiveness of different classes of medication, and for different medications within classes?

    c. What is the evidence of differential effectiveness of different psychotherapy approaches, delivery mode, and components of psychotherapy for childhood anxiety disorders that are necessary and sufficient for improvement (including number of treatments and intensity of psychotherapy)?

    d. How does comparative effectiveness of interventions vary according to child/family characteristics, disease characteristics, including age, sex, race, ethnicity, SES, diagnosis, child maltreatment, parent/family comorbidity, duration, maltreatment?

    e. How does comparative effectiveness of interventions vary according to child comorbid conditions, including Attention Deficit Hyperactivity Disorder (ADHD), depression, substance abuse, autism spectrum disorder, behavioral disorders and somatic medical conditions?

    f. What are the treatment burdens (for patients, providers, and health systems) and contextual factors (patient/family preference, time associated with psychotherapy) that influence treatment choices for childhood anxiety disorders?

KQ2: What are the comparative harms and safety concerns regarding the available treatments for childhood anxiety disorders, including panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder, and separation anxiety?

    a. What is the evidence for short-term and long-term patient experienced harms associated with treatments for childhood anxiety disorders?

Population, Interventions, Comparators, Outcomes, Timings, and Settings (PICOTS) by Key Question (KQ)

KQ1: Effectiveness
- Population: Children and adolescents between 3 and 18 years old with panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder, and separation anxiety.
- Interventions: Any psychotherapy, pharmacotherapy, alone or combined

- Pharmacological treatments will include all formulations of:
  - Selective reuptake inhibitor (SRI)
    - Citalopram (Celexa)
    - Escitalopram (Lexapro)
    - Fluoxetine (Prozac)
    - Fluvoxamine (Luvox)
    - Paroxetine (Paxil)
    - Sertraline (Zoloft)
  - Serotonin-norepinephrine reuptake inhibitors (SNRI)
    - Desvenlafaxine (Pristiq)
    - Duloxetine (Cymbalta)
    - Venlafaxine (Effexor)
  - TCAs
    - Amiptriptyline or Nortriptyline (Elavil or Aventyl HCI)
    - Clomipramine (Anafranil)
  - Benzodiazepines
    - Alprazolam (Xanax, Niravam)
    - Clonazepam (Klonopin)
    - Lorazepam (Ativan)
  - Atypical Antipsychotics
    - Aripiprazole (Abilify)
    - Olanzapine (Zyprexa Zydis)
    - Quetiapine (Seroquel)
    - Risperidone (Risperdal)
    - Ziprasidone (Geodon, Zeldox, or Zipwell)
  - Monoamine oxidase inhibitor
    - Phenelzine (Nardil)
  - Others
    - Bupropion (Wellbutrin)
    - Mirtazapine (Remeron)
    - D-Cycloserine (Seromycin)
    - N-Acetylcysteine
    - Methylphenidate (Ritalin, Daytrana, Concerta, Methylin, or Aptensio)
    - Riluzole (Rilutek)
    - Buspirone (Buspar)
    - Propranolol (Inderal, Hemangeol, or Innopran)
    - Prazosin (Minipress)
    - Cyproheptadine (Periactin or Peritol)
    - Carbamazepine (Tegretol, Carbatrol, Equetro, or Epitol)
    - Divalproex (Alti-Valproic, Depakote, Depakote DR, Depakote ER, or Depakote Sprinkles)
- Psychotherapies:
  - Cognitive and behavioral therapies (CBT)

- Exposure Therapy/Systematic Desensitization
  - Contingency Management Exposure Therapy
  - Self-Control Exposure Therapy
- Family Focused Cognitive Behavior Therapy
- Child Focused Cognitive Behavior Therapy
  - Parent Child Interaction Therapy
  - Problem solving therapy (PST)
  - Third wave (Mindfulness) therapies
    - Acceptance and Commitment Therapy
    - Mindfulness Based Cognitive Therapy/Mindfulness Based Stress Reduction
  - Psychodynamic psychotherapy
    - Interpersonal psychotherapy (IPT)
    - Play therapy
  - Family therapy
    - Behavioral Systems Family therapy
    - Narrative Family Therapy
    - Solution Focused Family Therapy
    - Strategic Family Therapy
  - Attention modification program
  - Motivational interviewing
  - Eye movement desensitization reprocessing therapy (EMDR)
  - Complementary psychotherapy techniques
    - Exercise
    - Biofeedback
    - Relaxation Therapies
      - Progressive muscle relaxation
      - Diaphramatic breathing
      - Visualization
      - Meditation techniques
    - Hypnosis

- Or any combined of the listed treatment
- Comparators:
  - Other treatment
  - Control conditions (education support, attention placebo)
  - Placebo
  - No treatment

- Outcomes:
  - Intermediate outcomes:
    - Standardized measures (child, parent, school, and clinician versions): the Screen for Anxiety-Related Emotional Disorders (SCARED), the Revised Children's Manifest Anxiety Scale (RCMAS), the Beck Anxiety Inventory, the Multidimensional

Anxiety Scale for Children (MASC), the Liebowitz Social Anxiety Scale, the Social Phobia and Anxiety Inventory for Children, the Spence Children's Anxiety Scale (child and parent report) (SCAS), Fear Survey Schedule for Children – Revised, Stait Trait Anxiety Inventory - Child (STAIC), Anxiety Disorder Interview Schedule - Child Version, Pediatric Anxiety Rating Scale (PARS), Child Behavior Checklist (CBCL), Revised Child Anxiety and Depression Scale (RCADS), Pre-School Anxiety Scale, Clinical Global Impression Scale (CGI), Children's Anxiety Meter-State (CAM-S)

- o Patient centered outcomes:
  - Remission, relapse, anxiety symptoms, behavioral problems (Behavior Assessment System for Children, Achenbach Child Behavior Checklist), parental overprotection, accommodation, parent distress, therapeutic alliance, school attendance, reduction in impairment (Child Sheehan Disability Scale), quality of life (Multidimensional Child Health Questionnaire, and Youth Quality of Life Instrument – Research Version), avoiding hospitalization, length of treatment, availability of treatment, peer relationship, functional impairment (Child Anxiety Impact Scale (CAIS), Children's Global Assessment Scale (CGAS), and Child Anxiety Life Interference Scale (CALIS)), avoidance behavior in children.

- Timings: Any
- Settings: Any
- Subgroups:
  - o Child and family characteristics:
    - Age group (3-6, 7-12, 13-18)
    - Sex (female, male)
    - Race/ethnicity (Caucasian, African American, Hispanic, Asian, and others)
    - SES (household income, parent education level)
      - Household income (below $24,300, between $24,300 and $48,600, between $48,600 and $97200, and above $97200)
      - Parent education level (less than high school or high school graduate, some college, and college graduate)
    - Family dysfunction/stressor:
      - Parenting Stress Index (PSI)
      - Brief Family Assessment Measure (FAM)
    - History of maltreatment (physical abuse, sexual abuse, emotional abuse, neglect, parental over-protection)

  - o Diagnosis:
    - Panic disorder
    - Social anxiety disorder
    - Specific phobias
    - Generalized anxiety disorder

- Separation anxiety)
- o Severity (CGI <6, CGI>=6)
- o Duration of treatment (<2 months, 2-6 months, >6 months)
- o Intensity of treatment (low, medium, high)
- o Patient/family preference (patient preferred, family preferred, and physician preferred)
- o Length of follow-up (<6 months, >=6 months)
- o Treatment sequence:
  - Treatment non-responders
  - Treatment naive
- o Comorbidities:
  - ADHD
  - Depression
  - Somatic medical conditions
  - Substance abuse
  - Autism
  - Obsessive-compulsive disorder (OCD)
  - Oppositional defiant disorder (ODD)
  - Conduct problems
  - Aggression
- o Provider:
  - Primary care physicians
  - Pediatrician
  - Psychologist
  - Psychiatrist
  - Nursing interventions, mid-level providers
- o Delivery mode:
  - Individual-based
  - Group-based
  - Technology-based
- o Type of studies (pragmatic, exploratory)
- o Settings:
  - Inpatient
  - Outpatient
  - Primary care
  - Mental health care

KQ2: Safety
- Population: Children and adolescents between 3 and 18 years old with any type of anxiety disorders.
- Interventions: Any psychotherapy, pharmacotherapy, complementary medicine approaches, alone or combined
  - o Pharmacological treatments will include all formulations of:
    - Selective reuptake inhibitor (SRI)
   - Citalopram (Celexa)
      - Escitalopram (Lexapro)

- Fluoxetine (Prozac)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
  - Serotonin-norepinephrine reuptake inhibitors (SNRI)
    - Desvenlafaxine (Pristiq)
    - Duloxetine (Cymbalta)
    - Venlafaxine (Effexor)
  - TCAs
    - Amiptriptyline or Nortriptyline (Elavil or Aventyl HCI)
    - Clomipramine (Anafranil)
  - Benzodiazepines
    - Alprazolam (Xanax, Niravam)
    - Clonazepam (Klonopin)
    - Lorazepam (Ativan)
  - Atypical Antipsychotics
    - Aripiprazole (Abilify)
    - Olanzapine (Zyprexa Zydis)
    - Quetiapine (Seroquel)
    - Risperidone (Risperdal)
    - Ziprasidone (Geodon, Zeldox, or Zipwell)
  - Monoamine oxidase inhibitor
    - Phenelzine (Nardil)
  - Others
    - Bupropion (Wellbutrin)
    - Mirtazapine (Remeron)
    - D-Cycloserine (Seromycin)
    - N-Acetylcysteine
    - Methylphenidate (Ritalin, Daytrana, Concerta, Methylin, or Aptensio)
    - Riluzole (Rilutek)
    - Buspirone (Buspar)
    - Propranolol (Inderal, Hemangeol, or Innopran)
    - Prazosin (Minipress)
    - Cyproheptadine (Periactin or Peritol)
    - Carbamazepine (Tegretol, Carbatrol, Equetro, or Epitol)
    - Divalproex (Alti-Valproic, Depakote, Depakote DR, Depakote ER, or Depakote Sprinkles)
- Psychotherapies
  - Cognitive and behavioral therapies (CBT)
    - Exposure Therapy/Systematic Desensitization
      - Contingency Management Exposure Therapy
      - Self-Control Exposure Therapy
    - Family Focused Cognitive Behavior Therapy

- Child Focused Cognitive Behavior Therapy
  - Parent Child Interaction Therapy
  - Problem solving therapy (PST)
  - Third wave (Mindfulness) therapies
    - Acceptance and Commitment Therapy
    - Mindfulness Based Cognitive Therapy/Mindfulness Based Stress Reduction
  - Psychodynamic psychotherapy
    - Interpersonal psychotherapy (IPT)
    - Play therapy
  - Family therapy
    - Behavioral Systems Family therapy
    - Narrative Family Therapy
    - Solution Focused Family Therapy
    - Strategic Family Therapy
  - Attention modification program
  - Motivational interviewing
  - Eye movement desensitization reprocessing therapy (EMDR)
  - Complementary psychotherapy techniques
    - Exercise
    - Biofeedback
    - Relaxation Therapies
      - Progressive muscle relaxation
      - Diaphramatic breathing
      - Visualization
      - Meditation techniques
    - Hypnosis
  - Or any combined of the listed treatment
- Comparators:
  - Other treatment
  - Control conditions (education support, attention placebo)
  - Placebo
  - No treatment
- Outcomes:
  - Safety outcomes:
    - Pediatric Adverse Event Rating Scale and other scales, incidence of any adverse events, GI adverse effects/discomfort, withdrawal symptoms, dropouts due to adverse events, neurological complaints, increase motor activity, suicidal ideation, homicidal behavior, treatment emergent suicidality, addiction, self-injurious behaviors, activation issues (e.g. sleep, motor activity), agitation, akathisia, mania, aggression, and psychosis.
- Timings: Any
- Settings: Any

III. Analytic Framework

Figure 1. Provisional analytic framework
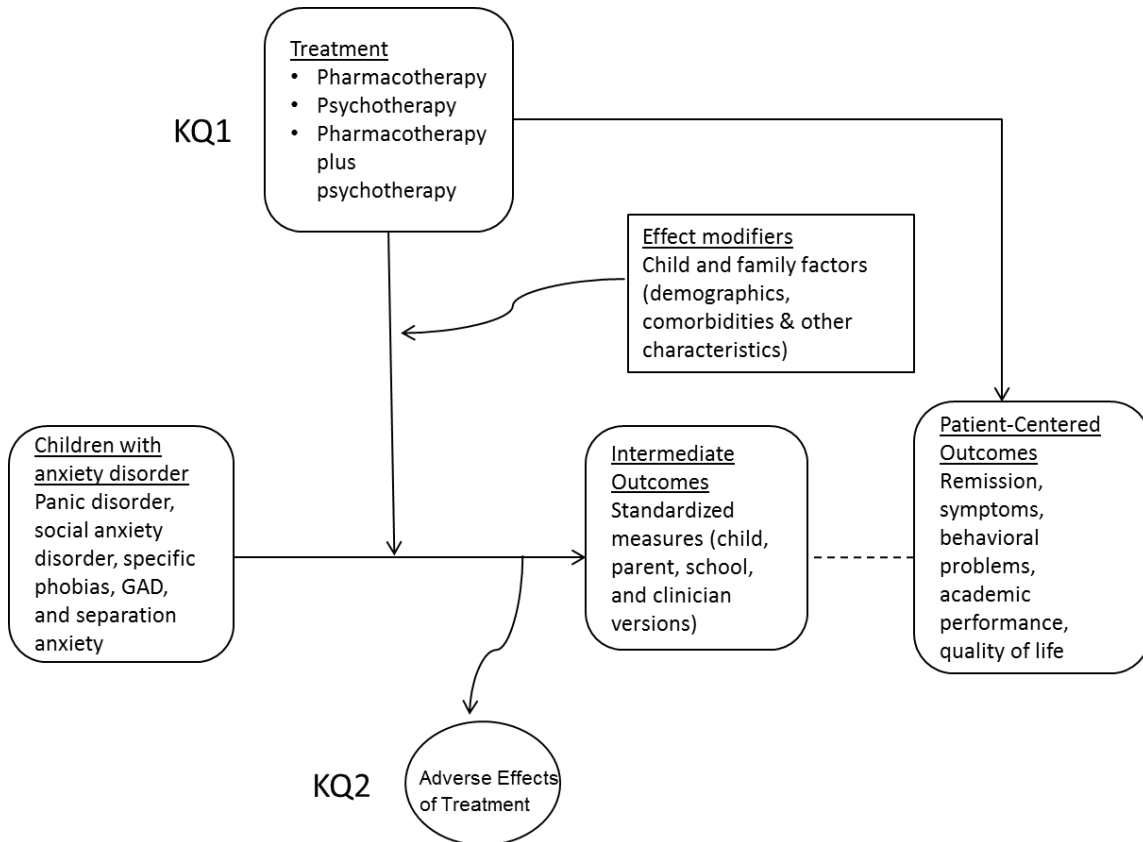
IV. Methods

To conduct this systematic review, the Evidence-based Practice Center (EPC) will follow the established methodologies as outlined in the Evidence-based Practice Center (EPC) Methods Guide for Comparative Effectiveness Reviews[25].

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

We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1).

Table 1. Inclusion and exclusion criteria

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Populations	• Humans • Children and adolescents between 3 and 18 years old • Patients with confirmed diagnosis of panic disorder, social anxiety disorder, specific phobias, generalized	• Animals • Adults (age >= 18 years) • Infants (age < 3 years) • Patients without confirmed diagnosis of panic disorder, social anxiety disorder, specific phobias, generalized

	anxiety disorder, or separation anxiety	anxiety disorder, or separation anxiety
Interventions	Any psychotherapy, pharmacotherapy, alone or combined: • Pharmacological treatments will include all formulations of: • Selective reuptake inhibitor (SRI): Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac), Fluvoxamine (Luvox), Paroxetine (Paxil), Sertraline (Zoloft) • Serotonin-norepinephrine reuptake inhibitors (SNRI): Desvenlafaxine (Pristiq), Duloxetine (Cymbalta), Venlafaxine (Effexor) • Tricyclic antidepressants (TCA): Amiptriptyline or Nortriptyline (Elavil or Aventyl HCl), Clomipramine (Anafranil) • Benzodiazepines: Alprazolam (Xanax, Niravam), Clonazepam (Klonopin), Lorazepam (Ativan) • Atypical Antipsychotics: Aripiprazole (Abilify), Olanzapine (Zyprexa Zydis), Quetiapine (Seroquel), Risperidone (Risperdal), Ziprasidone (Geodon, Zeldox, or Zipwell) • Monoamine oxidase inhibitor: Phenelzine (Nardil) • Others: Bupropion (Wellbutrin), Mirtazapine (Remeron), D-Cycloserine (Seromycin), N-Acetylcysteine,	None

	Methylphenidate (Ritalin, Daytrana, Concerta, Methylin, or Aptensio), Riluzole (Rilutek), Buspirone (Buspar), Propranolol (Inderal, Hemangeol, or Innopran), Prazosin (Minipress), Cyproheptadine (Periactin or Peritol), Carbamazepine (Tegretol, Carbatrol, Equetro, or Epitol), Divalproex (Alti-Valproic, Depakote, Depakote DR, Depakote ER, or Depakote Sprinkles)
	• Psychotherapies:
	• Cognitive and behavioral therapies (CBT)
	   o Exposure Therapy/Systematic Desensitization
	• Contingency Management Exposure Therapy
	• Self-Control Exposure Therapy
	   o Family Focused Cognitive Behavior Therapy
	   o Child Focused Cognitive Behavior Therapy
	• Parent Child Interaction Therapy
	• Problem solving therapy (PST)
	• Third wave (Mindfulness) therapies
	   o Acceptance and Commitment Therapy
	   o Mindfulness Based Cognitive Therapy/Mindfulness Based Stress Reduction
	• Psychodynamic psychotherapy
	   o Interpersonal psychotherapy (IPT)	

	o Play therapy • Family therapy o Behavioral Systems Family therapy o Narrative Family Therapy o Solution Focused Family Therapy o Strategic Family Therapy • Attention modification program • Motivational interviewing • Eye movement desensitization reprocessing therapy (EMDR) • Complementary psychotherapy techniques o Exercise o Biofeedback o Relaxation Therapies • Progressive muscle relaxation • Diaphramatic breathing • Visualization • Meditation techniques o Hypnosis • Or any combined of the listed treatment	
Comparators	Other treatment or no treatment	None
Outcomes	KQ 1: • Intermediate outcomes: Standardized measures (child, parent, school, and clinician versions): the Screen for Anxiety-Related Emotional Disorders (SCARED), the Revised Children's Manifest Anxiety Scale (RCMAS), the Beck Anxiety Inventory, the Multidimensional Anxiety Scale for Children (MASC), the Liebowitz Social Anxiety Scale, the Social Phobia and Anxiety Inventory for Children, the Spence	None

	Children's Anxiety Scale (child and parent report) (SCAS), Fear Survey Schedule for Children – Revised, Stait Trait Anxiety Inventory - Child (STAIC), Anxiety Disorder Interview Schedule - Child Version, Pediatric Anxiety Rating Scale (PARS), Child Behavior Checklist (CBCL), Revised Child Anxiety and Depression Scale (RCADS), Pre-School Anxiety Scale, Clinical Global Impression Scale (CGI), Children's Anxiety Meter-State (CAM-S) • Patient centered outcomes: • Remission, relapse, anxiety symptoms, behavioral problems (Behavior Assessment System for Children, Achenbach Child Behavior Checklist), parental overprotection, accommodation, parent distress, therapeutic alliance, school attendance, reduction in impairment (Child Sheehan Disability Scale), quality of life (Multidimensional Child Health Questionnaire, and Youth Quality of Life Instrument – Research Version), avoiding hospitalization, length of treatment, availability of treatment, peer relationship, functional impairment (Child Anxiety Impact Scale (CAIS), Children's Global Assessment Scale (CGAS), and Child Anxiety Life Interference Scale (CALIS)),	

	avoidance behavior in children. KQ 2: • Safety outcomes: Pediatric Adverse Event Rating Scale and other scales, incidence of any adverse events, GI adverse effects/discomfort, withdrawal symptoms, dropouts due to adverse events, neurological complaints, increase motor activity, suicidal ideation, homicidal behavior, treatment emergent suicidality, addiction, self-injurious behaviors, activation issues (e.g. sleep, motor activity), agitation, akathisia, mania, aggression, and psychosis.	
Timing	Any	None
Settings	Any	None
Study design	• Original data • Any sample size • RCTs, nonrandomized comparative studies (prospective and retrospective) • Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	• In vitro studies • Non-original data (e.g. narrative reviews, editorials, letters, or erratum) • Non-comparative observational studies, case series
Publications	Any	None
Abbreviations: KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial		

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

We plan to conduct a comprehensive literature search of eight databases, including Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R), EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and SciVerse Scopus from databases inception to the

present. We have developed a preliminary database search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We will use relevant systematic reviews and meta-analysis to identify additional existing and new literature. We will also search U.S. Food and Drug Administration (FDA) new drug applications, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. We sought input from the Technical Expert Panel (TEP) on refining literature search strategy. The search strategy will be peer-reviewed by an independent information specialist. An experienced librarian will conduct the search. All citations identified through the process will be imported to a reference management system ((EndNote® Version X4; Thomson Reuters, Philadelphia, PA).

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

C. Data Abstraction and Data Management

At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, interventions, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form will be pilot-tested by all study team members using 10 randomly selected studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. A second reviewer will randomly select studies, review data extraction, and resolve conflicts. DistillerSR will also be used to create data extraction forms and facilitate data extraction.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will evaluate the risk of bias of each included study using predefined criteria. For RCTs, we plan to apply the Cochrane Collaboration's Risk of Bias tool to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias[26]. For observational studies, we will select appropriate items from the Newcastle-Ottawa Scale[27]. Additional criteria will be adopted from other quality appraisal tools if deemed appropriate.

E. Data Synthesis

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

We will determine whether meta-analysis is appropriate (i.e., more than 2 trials address the same PICOTS and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. If meta-analysis is deemed appropriate, we plan to use the DerSimonian and Laird random effect method to combine direct comparisons between treatments if the number of studies included in the analysis is larger than 18[28]; otherwise, the DerSimonian and Laird random effect method with the Knapp and Hartung adjustment of the variance will be adopted[29]. We will evaluate heterogeneity between studies using I2 indicator.

We will evaluate the feasibility of conducting network meta-analysis to combine direct and indirect comparisons and provide ranking of treatments in terms of efficacy and safety. Conducting network meta-analysis requires satisfying three assumptions, homogeneity of the direct estimates, consistency between direct and indirect estimates, and transitivity. Depending on the geometry of networks [closed loop (with direct estimates available) vs. open (unconnected nodes)], number of comparisons, and number of studies, we will adjust the analysis plan. Frequentist approach based on Ian White's meta-regression or multivariate random effects model will be used if we identify a large number of studies with at least one closed loop in the network[30]. Otherwise, a Bayesian approach based on Lu and Ades method will be used[31]. Consistency of network meta-analysis will be evaluated using side-splitting models. In addition, we will conduct sensitivity analyses whenever different approaches or assumptions are in question.

We will evaluate potential publication bias by evaluating funnel plots symmetry and using statistical tests such as Egger linear regression test if the number of studies included in a direct comparison is large (n>=20).

We may utilize existing systematic reviews based on the presence of high volume of trials, and the availability of high-quality, comprehensive evidence reviews for this topic identified during topic refinement. We will follow the AHRQ EPC guidance on using existing systematic reviews[25, 32]. Systematic reviews will be used if they address a key question, include studies that meet the PICOTS as defined above, and are assessed as being sufficiently credible, according to the AMSTAR quality assessment tool[33, 34]. If systematic reviews are included, we will update findings with any new primary studies identified in our searches. We will update meta-analyses. If multiple eligible systematic reviews are relevant and credible, we will focus on the findings from the most recent ones and evaluate areas of consistency and inconsistency across the reviews[25, 32].

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

We will grade the strength of the body of evidence as per the EPC methods guide on assessing the strength of evidence. A body of evidence consisting from randomized trials start as high strength of evidence and a body of evidence consistent of observational studies start as low strength of evidence[25]. Following the standard EPC approach, for each comparison and for the critical outcome, we will assess the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of

evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates); the consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

Based on this assessment and the initial study design, we will assign a strength of evidence rating as high, moderate, low, or 'insufficient evidence to estimate an effect'. We will produce summary of evidence tables that will provide for each comparison and for each outcome: data source, effect size, strength of evidence rating; and rationale for judgments made on each domain of evidence rating.

G. Assessing Applicability

We will follow the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies[25]. Applicability for each outcome will be summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. We will focus on whether the populations, interventions, and comparisons in existing studies are representative of current practice. We will select a limited number of the most important factors that may affect applicability (including the age group of the population, setting, and comorbidities) and systematically abstract such factors and evaluate their impact on how applicable the evidence is to the question of interest. We will report any limitations in applicability of individual studies in evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

V. References

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VI. Definition of Terms

ACT   Acceptance and Commitment Therapy

ADHD   Attention Deficit Hyperactivity Disorder

AHRQ   Agency for Healthcare Research and Quality

APA   American Psychological Association

AACAP   American Academy of Child & Adolescent Psychiatry

CBT   Cognitive Behavioral Therapy

EMDR   Eye Movement Desensitization Reprocessing therapy

EPC   Evidence-based Practice Center

FDA   U.S. Food and Drug Administration

IPT   Interpersonal Psychotherapy

MASC   Multidimensional Anxiety Scale for Children

MHRA   Medicines and Healthcare Products Regulatory Agency

NICE   National Institute for Health and Care Excellence

NIMH   National Institute of Mental Health

KQ   Key Question

OCD   Obsessive Compulsive Disorder

PCIT   Parent Child Interaction Therapy

PICOTS   Populations, Interventions, Comparators, Outcomes, Timing, and Settings

PTSD   Post-traumatic Stress Disorder

PST   Problem Solving Therapy

RCMAS   Revised Children's Manifest Anxiety Scale

RCT   Randomized Controlled Trial

SCARED   Screen for Anxiety-Related Emotional Disorders

SCAS   Spence Children's Anxiety Scale

SES   Socioeconomic Status

SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SRI	Selective Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STAIC	State-Trait Anxiety Inventory-Child Scale
TCA	Tricyclic Antidepressant
TEP	Technical Expert Panel

VII. Summary of Protocol Amendments

No protocol amendments to date.

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. Further refinement will be done based on feedback from 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 do not review 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 multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not conduct analysis of any kind nor do they contribute to the writing of the report. They do not review 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 is funded under Contract No. HHSA 290-2015-000131 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.

XIV. Registration

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