Evidence-based Practice Center Systematic Review Protocol

Project Title: ***Mindfulness-Based Interventions for Wellbeing and Mental Health in Children and Adolescents: A Systematic Review***

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(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

The 2020 National Survey of Children's Health (NSCH) reported that 8.5 percent of children aged 3 to 17 years had an anxiety disorder, and 3.8 percent had a depression disorder at the time of the survey.[1] Both conditions often co-occur, and their prevalence has risen over the past decade.[2] Children with chronic health conditions such as cancer, diabetes, and epilepsy have an increased risk of anxiety and depression.[2-5] The Centers for Disease Control and Prevention (CDC) reported that 40 percent of children aged 12 to 17 years in the United States have at least one chronic health condition.[6] This highlights the need for interventions for anxiety and depression, as well as for children and adolescents with chronic health conditions. Despite the high prevalence and burden of anxiety and depression, not all who need treatment receive it. For example, only about 48 percent of adolescents with depression received treatment in 2022.[7] This rate has remained relatively steady over the years. This low treatment rate is attributed to limited access to mental health services, societal stigma, and delays in diagnosis.[8-10] Treatment rates are particularly low among minority groups, including those experiencing poverty, those in foster care, individuals identifying as lesbian, gay, bisexual, transgender, queer/questioning, and Black, Asian, and Hispanic. These individuals face stark contrasts in treatment access compared with their peers from other backgrounds.[11-14]

Effective preventive and treatment options for anxiety and depression in children and adolescents are important for immediate wellbeing, as well as for promoting positive long-term outcomes in many aspects of life.[9,15,16] However, many conventional interventions, such as pharmacotherapy, are limited by side effects and access, necessitating additional approaches.

Mindfulness involves focusing attention on the present moment and accepting what is without judgment.[17] Mindfulness-based interventions (MBIs) present a promising option for (1) preventing anxiety and depression in subclinical individuals, (2) reducing anxiety and depression symptom severity in diagnosed individuals, and (3) serving a dual function of improving mental health outcomes and symptoms of chronic physical conditions.[18-24]

While contemporary guidelines in the United States primarily focus on conventional treatments for anxiety and depression (e.g., behavioral interventions, pharmacotherapy),[25,26] these approaches may not sufficiently address the needs of all children and adolescents. Additional, existing systematic reviews evaluating MBIs are outdated and limited in their focus (e.g., concentrating only on anxiety or school-based interventions).[27-35] Though the American Academy of Pediatrics

(AAP) evaluated a number of MBIs; the publication is outdated and lacks systematic rigor.[21] Given the growing interest in MBIs and their potential benefits across broad, varied settings, a comprehensive and up-to-date systematic review is essential to guide evidence-based healthcare and expand our understanding of MBIs benefits and harms.

Purpose of the Review

This systematic review will assess the effectiveness and potential harms of MBIs in children and adolescents, used for the prevention or treatment of mental health conditions and for improving general wellbeing. This systematic review is intended to support the development of clinical practice guidelines. The intended audience includes guideline developers, health system administrators, and clinicians who provide care to children and adolescents (e.g., primary care providers, advanced practice practitioners, and psychologists).

II. Key Questions

The original Key Questions (KQs) were posted on the AHRQ website between November 14 and January 5, 2023 for public comments. These questions were: **KQ 1**. What are the benefits and harms of mindfulness-based interventions for mental health in the general child and adolescent populations? **KQ 2**. What are the benefits and harms of mindfulness-based interventions for mental health in children and adolescents diagnosed with anxiety or depression? **KQ 3**. What are the benefits and harms of mindfulness-based interventions for mental health in children and adolescents with a chronic condition who are at risk for elevated symptoms of anxiety and depression? The American Psychological Association suggested expanding KQ1 to include children with behavioral disorders, advocating for a broader evaluation of MBIs. Additionally, there was a call to refine KQ1 to specify whether it includes various mindfulness activities in settings such as schools and homes. For KQ2, the focus was recommended to be on "targeted" or "intensive" interventions aligned with explicit treatment goals. Lastly, KQ3 feedback sought clarity on whether the question addresses the prevention or treatment of anxiety and depression among those with chronic physical conditions. We also held discussions with seven Key Informants (KIs), who provided overall feedback that the target of this review is important and primarily regarded specifics of interventions, comparators, and populations, advocating for careful consideration of delivery methods, potential barriers, facilitators, and the need for culturally sensitive and inclusive approaches. Based on the feedback that MBIs are thought to improve multiple aspects of life, the phrase "for mental health" was removed from all KQs as outcomes were not limited to mental health. We also held discussions with six members of our Technical Expert Panel (TEP). In general, TEP expressed no concerns or suggestions for the updated KQs and no further changes were made. The KQs for this review are:

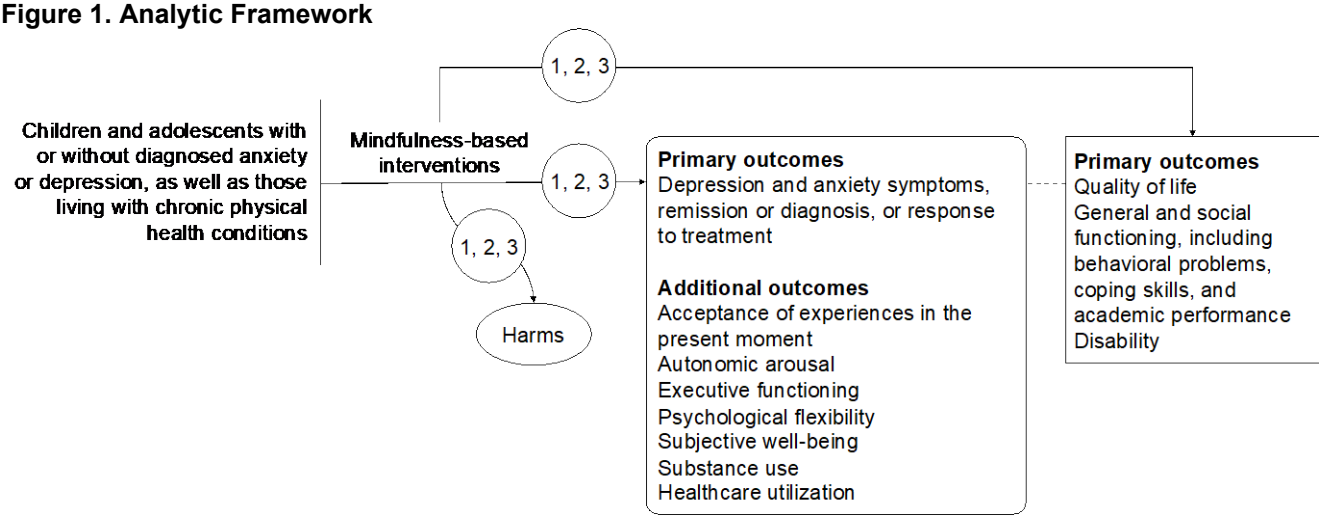
Key Question 1. What are the benefits and harms of mindfulness-based interventions in the general child and adolescent populations?

Key Question 2. What are the benefits and harms of mindfulness-based interventions in children and adolescents diagnosed with anxiety and/or depression?

Key Question 3. What are the benefits and harms of mindfulness-based interventions in children and adolescents with a chronic condition who are at risk for elevated symptoms of anxiety and/or depression?

III. Logic Model

Figure 1. Analytic Framework



Circles denote Key Question numbers.

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review (UPDATED):

For the purpose of this review, the intervention must include three components: (1) a repeated practice with any modality (e.g., in-person, virtual, a hybrid), (2) focused on the development of nonjudgmental self-regulation of attention maintained on immediate experience, and (3) delivered by a person (e.g., clinician, social worker, educator) with some training in mindfulness. We will include studies that report at least one primary outcome.

Table 1. Preliminary PICOTS criteria

	Inclusion Criteria	Exclusion Criteria
Population	**KQ 1.** Children and adolescents aged 3 to 18 years *without* known anxiety and depression **KQ 2.** Children and adolescents aged 3 to 18 years *with* a diagnosis of depression or anxiety **KQ 3**. Children and adolescents aged 3 to 18 years *with* a chronic condition who are at risk for elevated symptoms of or being diagnosed with anxiety and depression Definition of chronic physical conditions: Medical physical conditions (i.e., conditions that primarily affect the body's systems and functions) that persist for one year or longer and require ongoing medical attention, limit activities of daily living, or both.	Studies with ≥20% of participants in the following groups and do not report findings by population • In institutions (e.g., psychiatric inpatients, long-term care facilities) • Diagnosed with advanced neurodevelopmental disorders (e.g., severe autism spectrum disorders [for example, level 3 on DSM-5], severe attention-deficit/hyperactivity disorder [e.g., based on DSM-5 definition], severe learning disorders [e.g., more than 2 standard deviations below the mean in one or more areas of cognitive processing related to the specific learning disorder]) • With major behavioral or emotional dysregulation (e.g., conduct disorder, oppositional defiant disorder, disruptive mood dysregulation disorder)[a]

	Inclusion Criteria	Exclusion Criteria
		• With substance use disorder We will exclude studies with MBIs designed and/or administered only to parents/caregivers, as well as interventions administered by parents/caregivers. We will exclude studies designed to treat test or sports performance anxiety, anxiety associated with medical/dental procedures and with interventions for specific high-risk exposures such as for post-sexual assault or another traumatic event.
Interventions	**KQ 1–3** In addition to the minimum requirements identified above: • Mindfulness-based intervention, provided alone or in addition to other therapies • Mindfulness is the primary component for multicomponent interventions (as a part of behavioral and similar non-pharmacological strategies), meaning that the intervention must be centered around mindfulness (e.g., the majority of the sessions or focus are mindfulness-based). • A mindfulness instructor (e.g., therapist, teacher) must have some training in providing mindfulness. We do not specify the required minimum training. • Clear specification of repeated practice (e.g., more than one session with an instructor, or repeated self-directed exercises after at least one initial session with an instructor). Examples of other therapies include structured mindfulness programs and mindfulness-based therapies such as: • Mindfulness-based Stress Reduction • Mindfulness-based Cognitive Therapy • Acceptance and Commitment Therapy Components of programs, if they are intentionally used to promote mindfulness principles and meet other criteria, may include: • Relaxation techniques • Meditation • Mindful breathing • Guided imagery • Visualization	Pharmacologic interventions or traditional psychotherapies alone (e.g., cognitive-behavioral therapy, play therapy, dialectical behavior therapy, parent-child interaction therapy) and integrative therapies alone including acupuncture/acupressure, expressive therapies, exercise, yoga, Tai Chi, biofeedback, hypnotherapy, massage, chiropractic care, homeopathy, diets (e.g., gluten-free diet), traditional Chinese medicine, Ayurveda.
Comparators	**KQ 1.** Usual care, enhanced usual care, waitlist control, sham, attention control, or no active intervention. **KQ 2–3.** Usual care, enhanced usual care, waitlist control, sham, attention control, no active intervention, or conventional therapies (i.e., pharmacotherapy for anxiety and/or depression, behavioral interventions[b])	Other mindfulness-based interventions (i.e., comparative effectiveness of MBIs). Other interventions not listed in the "included" list.
Outcomes	**KQ 1–3** **Primary outcomes** (children and adolescent outcomes) • Quality of life (e.g., PedsQL, KIDSCREEN, CHQ, ITQOL, PQ-LES-Q) • General and social functioning (e.g., SDQ, SSIS, CGI-I, CGAS), including behavior problems (e.g., ECBI, CBCL, SDQ), coping skills (e.g., CSI-CA, CCSC, RSQ), executive functioning (e.g., BRIEF), academic performance (e.g., WIAT, Woodcock-Johnson Tests of Achievement) • Disability (e.g., VABS, FDI, days of missed school)	Other outcomes, patient/caregiver outcomes

	Inclusion Criteria	Exclusion Criteria
	• Depression (e.g., CDI, BDI, MFQ, CES-D, CDRS-R, RADS, PHQ-A, PI-ED), diagnosis (KQs 2 and 3 only), and remission and response (KQs 1 and 3) • Anxiety (e.g., SCARED, MASC, SCAS, CAIS, GAD-7, PHQ-A, PI-ED), diagnosis (KQs 2 and 3 only), and remission and response (KQs 1 and 3) • Any reported adverse events or unintended negative consequences attributed to treatment **Additional outcomes** (children and adolescent outcomes) • Acceptance of experiences in the present moment (e.g., CAMM) • Autonomic arousal (e.g., SCL, HRV) • Executive functioning (e.g., BRIEF) • Subjective well-being (e.g., PANAS-C, SLSS) • Substance use • Psychological flexibility (e.g., AFQ-Y, AAQ) • Healthcare utilization	
Timing	• A minimum of 4 weeks since the beginning of the intervention or baseline assessment (if the intervention start cannot be determined) for all outcomes except for harms. • We will extract harms reported at any followup, regardless of the duration since the intervention start or baseline assessment.	Mid-intervention assessment times
Setting	**KQ 1–3** • Administered in outpatient health care or community settings (e.g., schools, residential) • Trials conducted in countries rated as "very high" on the 2019 Human Development Index (as defined by the United Nations Development Program)	In-patient, ED/EMS, and psychiatric subacute settings (e.g., partial hospitalization programs, intensive outpatient programs)
Study Design	• Randomized controlled trials (individually or site-randomized), with individually randomized trials reporting outcomes for a minimum of 10 participants per treatment arm • Period 1 data from crossover RCTs • Published in English-language • Published in 2009 or later	Other

Abbreviations: AAQ = Acceptance and Action Questionnaire; AFQ-Y = Avoidance and Fusion Questionnaire for Youth; BDI = Beck Depression Inventory; BRIEF = Behavior Rating Inventory of Executive Function; CAIS = Child Anxiety Impact Scale; CAMM = Child and Adolescent Mindfulness Measure; CBCL = Child Behavior Checklist; CCSC = Children's Coping Strategies Checklist; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale–Revised; CES-D = Center for Epidemiologic Studies Depression Scale; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impression-Improvement Scale; CHQ = Child Health Questionnaire; CSI-CA = Coping Strategies Inventory for Children and Adolescents; ED/EMS = emergency department /emergency medical services; ECBI = Eyberg Child Behavior Inventory; FDI = Functional Disability Inventory Child Form; GAD-7 = Generalized Anxiety Disorder scale; HRV = heart rate variability; ITQOL = Infant/Toddler Quality of Life Questionnaire; KQ = Key Question; MASC = Multidimensional Anxiety Scale for Children; MFQ = Mood and Feelings Questionnaire; NA = not applicable; PedsQL = Pediatric Quality of Life Inventory; PHQ-A = Patient Health Questionnaire for Adolescents; PICOTS = population, interventions, comparators, outcomes, timing, and setting; PI-ED = Paediatric Index of Emotional Distress; PQ-LES-Q = Perceived Quality of Life Scale; RADS = Reynolds Adolescent Depression Scale; RSQ = Responses to Stress Questionnaire; SCARED = Screen for Child Anxiety Related Emotional Disorders; SCAS = Spence Children's Anxiety Scale; SCL = Skin Conductance Level; SDQ = Strengths and Difficulties Questionnaire; SLSS = Students' Life Satisfaction Scale; SSIS = Social Skills Improvement System; PANAS-C = Positive and Negative Affect Schedule for Children; SWLS = Satisfaction with Life Scale; VABS = Vineland Adaptive Behavior Scales; WIAT = Wechsler Individual Achievement Test; WISC = Wechsler Intelligence Scale for Children

[a]These are reviewed in other AHRQ systematic reviews

[b]We defined behavioral interventions as nonpharmacologic strategies intended to enhance outcomes by modifying behavior and/or ways of thinking (e.g., cognitive behavioral therapy, coping skills training, behavioral therapy, biofeedback, dialectical behavioral therapy)

Table 2. Pharmacological options for general anxiety and major depressive disorder

Condition	Drug Class	Specific Drugs	FDA Approved Age Range for those aged ≤18 years	Usage (Children/ Adolescents)
Anxiety	Benzodiazepines	Alprazolam, clonazepam, lorazepam	Not approved for pediatric anxiety	Off-label
Anxiety	Azapirones	Buspirone	Not approved for pediatric anxiety	Off-label
Anxiety	TCAs	Imipramine, clomipramine	≥6 years for nocturnal enuresis (Imipramine), ≥10 for OCD (Clomipramine)	Off-label
Depression	Atypical Antidepressants	Bupropion	Not approved for pediatric depression	Off-label
Depression	TCAs	Amitriptyline, nortriptyline	Not approved for pediatric depression	Off-label
Anxiety/ Depression	SSRIs	Fluoxetine	≥8 years for depression, ≥7 for OCD	On-label for depression Off-label for anxiety
Anxiety/ Depression	SSRIs	Escitalopram	≥12 years for depression, and for GAD in adults	Off-label for anxiety
Anxiety/ Depression	SSRIs	Sertraline	≥6 years for OCD, ≥12 for depression, GAD in adults	On-label for depression Off-label for anxiety
Anxiety/ Depression	SNRIs	Duloxetine	≥7 years for GAD, ≥13 for MDD	On-label for GAD and MDD depression

Abbreviations: GAD = Generalized anxiety disorder; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; OCD = Obsessive-Compulsive Disorder; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Literature Search Strategies to Identify Relevant Studies to Answer the Key Questions (UPDATED):

Literature Databases: We will conduct a comprehensive database search, including Ovid MEDLINE®, PsycINFO®, and the Cochrane Library. In order to capture relevant literature relating to school-based interventions, we will also search the Education Resources Information Center (ERIC). Literature search dates will begin in 2009, per our PICOTS criteria.

Search Strategy: Appendix A contains our initial MEDLINE search strategy, developed by a research librarian with expertise in conducting searches for systematic reviews. The MEDLINE search strategy will be peer-reviewed by another EPC librarian using the Peer Review of Electronic Search Strategies (PRESS) instrument[36] and translated for use in the other databases. Modifications to the searches and additional search strategies will be considered in consultation with the TEP. Literature searches will be updated while the draft report is undergoing peer review and posted for public comment.

Supplemental Evidence and Data for Systematic review (SEADS). AHRQ will publish an announcement in the Federal Register to notify stakeholders about the opportunity to submit data or, studies to include in the review via the SEADS portal on the Effective Health Care Website.

Hand Searching. Reference lists of included articles and systematic reviews will be reviewed for additional relevant literature.

Contacting Author. In the event that important information regarding methods or results appears to be omitted from the published results of a study, we will attempt to contact the authors to obtain additional information.

Screening: We will use prespecified criteria to guide study selection. Citations will be screened in DistillerSR (DistillerSR Inc., Ottawa, Canada). To ensure uniformity in screening criteria application among investigators, we will conduct a norming exercise, wherein all reviewers will independently screen a common set of 10 to 20 articles. Two reviewers will independently screen abstracts and full-text articles. Discrepancies will be resolved by discussion and consensus among the review team. To optimize the efficiency of our screening process, we will begin by evaluating RCTs that our preliminary search identified as potentially relevant. By prioritizing these trials, we can quickly identify those with a high chance of inclusion. This will also help train DistillerSR's DAISY Artificial Intelligence classifier in title and abstract screening, resulting in more accurate prioritization of references for screening and faster ordering of full-text articles for potential inclusion. Once the tool estimates that 95% of relevant references have moved on to full-text screening, we may consider changing the screening approach from dual to single screening by experienced reviewers.

Data Abstraction and Data Management: One reviewer will extract data into a standardized data abstraction form in DistillerSR. A second reviewer will perform a quality check of the extracted data for completeness and accuracy. For each included trial, we will extract general study characteristics (e.g., authors, year of publication, design, purpose, country, funding source), patients' characteristics (e.g., age, sex, gender identification, race/ethnicity, socioeconomic status, comorbidities), setting (e.g., community, school, urban/rural)), anxiety and depression characteristics (e.g., diagnostic criteria used, severity), intervention and comparator details (e.g., name, type, dose, length of intervention, delivery method, MBI instructors' expertise/training, parent/caregiver involvement, concomitant treatments, other treatments), and study results (outcomes).

Assessment of Methodological Risk of Bias of Individual Studies: We define the risk of bias as the risk that a study's point estimate of the effect size is inaccurate. We will assess the risk of bias for each included study using the Cochrane Risk of Bias 2 (ROB2) tool to assess risk of bias in randomized trials.[37] The five domains of the tool are the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Two reviewers will independently evaluate each to-be-graded outcome reported by each study and assign a risk of bias rating of "high," "some concerns," or "low" for each of the above domains and the overall risk of bias. Discrepancies will be resolved by discussion and consensus among the review team. Although we will assess selective outcome reporting, we will not incorporate it in the overall risk of bias rating because the EPC strength of evidence (SOE) system places it in the Reporting Bias domain (along with publication bias).

Data Synthesis: The data will be synthesized separately for each KQ. When possible, we will summarize the evidence both qualitatively and quantitatively (e.g., meta-analysis, network meta-analysis). Our decision to conduct a quantitative synthesis depends on the number of studies, population, research design, and outcome measure heterogeneity.

To address potential clinical heterogeneity, we plan to conduct separate analyses for individuals at consolidated neurocognitive development stages: early childhood (3–8 years), middle childhood and early adolescence (9–14 years), and adolescence (15–18 years). With fewer, larger groups, we are more likely to gather sufficient evidence for each category to draw meaningful conclusions. Trials

included will report outcomes at various time points, which we will aggregate into the following intervals: 4 to <8 weeks, 8 to <12 weeks, 12 weeks to <6 months, 6 months to <12 months, and ≥12 months since the beginning of the intervention or baseline assessment (if the intervention start cannot be determined). Only outcome measurements taken after the intervention has been completed will be included in the synthesis.

If sufficient data are reported in the included studies, we will consider using a framework such as the Template for Intervention Description and Replication (TIDieR)[38] to standardize the synthesis of information about interventions, add clarity about differences and similarities between interventions, and help to elucidate which interventions and/or components of interventions are effective.

To assess effectiveness, we will tackle two interrelated tasks: evaluate the overall effectiveness of the interventions and evaluate the effects of single components. If the data permit, we plan to conduct a network meta-analysis (NMA), specifically focusing on the component NMA.[39] This method is particularly suitable for analyzing complex multicomponent interventions by breaking down each intervention into its components, which are clinically meaningful units. It also incorporates both direct and indirect evidence, provided they are consistent. If data do not allow an NMA, we will employ standard pairwise meta-analysis to summarize overall effectiveness and conduct subgroup analysis and meta-regression to estimate the effect of MBIs delivered via different modes (e.g., in-person, virtual care, mHealth) and formats (e.g., one-on-one, groups). To assess whether pairwise meta-analysis will be appropriate, we will consider population factors, including treatment history, intervention factors such as similarity in intervention definitions, and whether outcomes are the same or address the same concept. Further, we will use multiple approaches to address the complexity of these interventions. As a first step to discern the contributions of single components to the overall effectiveness of a combined intervention and variability in control groups, meta-regression models or hierarchical meta-regression models will be used.

The strength of evidence will be assessed as low, moderate, high, or insufficient, and the magnitude of the effect will be assessed according to Table 3. Estimates below the threshold for a small effect will be categorized as "no effect."[40,41] Results with a small, medium, or large effect that will not achieve statistical significance will be considered to have "potential effects" if the 95 percent confidence interval included meaningful (see Table 3) benefit or harm but will not be so wide that they included the potential for both meaningful benefits and harms.

Table 3. Definitions of effect sizes

Effect size	Definition
Small effect	MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale SMD 0.2 to 0.5 RR/OR 1.2 to 1.4
Moderate effect	MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale SMD >0.5 to 0.8 RR/OR 1.5 to 1.9
Large effect	MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale SMD >0.8 RR/OR ≥2.0

Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: We will grade the SOE for the following outcomes:

- Quality of life
- General and social functioning
- Disability
- Depression

- Anxiety
- Adverse events

We will grade the SOE based on the recommendations given in the EPC Methods Guide.[42] The assessment will consider several domains—the risk of bias, directness, consistency, precision, and reporting bias. In case they are relevant, additional domains, such as dose-response association and strength of association, will also be assessed. The SOE will be rated as high, moderate, low, or insufficient for each outcome of each comparison of each KQ. The SOE will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the included domains. The four levels are:

- High—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. The findings are stable (i.e., another study would not change the conclusions).
- Moderate—Confident that the effect estimate lies close to the true effect for this outcome. The body of evidence has some deficiencies. The findings are likely to be stable, but some doubt remains.
- Low—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). Additional evidence is needed before concluding that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient—No evidence. Investigators are unable to estimate an effect or have no confidence in the estimate of the effect of this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding a conclusion. We will assign a rating of Insufficient when the evidence does not permit a conclusion for the outcome of interest for that KQ (for example, when a difference is not statistically significant, and the 95% confidence is too wide to permit a conclusion that there is no important difference).

Below, we discuss the primary domains and how we will assess them:

Risk of bias (see the above section entitled *Assessment of Methodological Risk of Bias of Individual Studies*). This concerns internal validity: the extent to which post-treatment outcomes can be attributed to the treatments rather than other factors. If the evidence permits a conclusion, all else being equal, a set of studies at low risk of bias yields a higher SOE rating than a set of studies at moderate or high risk of bias.

Directness. Directness relates to (a) the extent to which evidence links interventions directly to a health outcome of specific importance for the review and (b) for comparative studies, whether the comparisons are based on head-to-head studies.

Consistency. Consistency is the degree to which included studies find either the same direction or similar magnitude of effect.

Precision. Precision is the degree of certainty surrounding an effect estimate concerning a given outcome, based on the width of confidence intervals relative to a clinically important effect estimate, sufficiency of sample size, and number of events.

Reporting bias. Reporting bias will be addressed by examining the funding source of included studies, the direction and magnitude of effects identified in included studies, possible selective

outcome reporting, and noting the presence of abstracts or ClinicalTrials.gov entries describing studies that did not subsequently appear as full-length published articles.

Assessing Applicability: We will assess applicability according to the approach described in the AHRQ Methods Guide.[42,43] We will use the PICOTS framework to consider the applicability of the evidence base for each key question; for example, examining the characteristics of the patient populations, interventions, and study settings.

Use of Artificial Intelligence and/or Machine Learning: We will use the DAISY Artificial Intelligence classifier in DistillerSR (DistillerSR Inc., Ottawa, Canada) to expedite screening. See the Screening section for details.

V. References

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VI. Definition of Terms

AAP = American Academy of Pediatrics; AAQ = Acceptance and Action Questionnaire; AFQ-Y = Avoidance and Fusion Questionnaire for Youth; BDI = Beck Depression Inventory; BRIEF = Behavior Rating Inventory of Executive Function; CAIS = Child Anxiety Impact Scale; CAMM = Child and Adolescent Mindfulness Measure; CBCL = Child Behavior Checklist; CCSC = Children's Coping Strategies Checklist; CDC = Centers for Disease Control and Prevention; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale–Revised; CES-D = Center for Epidemiologic Studies Depression Scale; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impression-Improvement Scale; CHQ = Child Health Questionnaire; CSI-CA = Coping Strategies Inventory for Children and Adolescents; ECBI = Eyberg Child Behavior Inventory; ED/EMS = emergency department /emergency medical services; ERIC = Education Resources Information Center; FDI = Functional Disability Inventory Child Form; GAD-7 = Generalized Anxiety Disorder scale; HRV = heart rate variability; ITQOL = Infant/Toddler Quality of Life Questionnaire; KIs = Key Informants; KQ = Key Question; KQs = Key Questions; MAOI = monoamine oxidase inhibitor; MASC = Multidimensional Anxiety Scale for Children; MBIs = mindfulness-based interventions; MD = mean difference; MFQ = Mood and Feelings Questionnaire; NA = not applicable; NMA = network meta-analysis; OCD = Obsessive-Compulsive Disorder; OR = odds ratio; PANAS-C = Positive and Negative Affect Schedule for Children; PHQ-A = Patient Health Questionnaire for Adolescents; PI-ED = Paediatric Index of Emotional Distress; PICOTS = population, interventions, comparators, outcomes, timing, and setting; PQ-LES-Q = Perceived Quality of Life Scale; PRESS = Peer Review of Electronic Search Strategies; PedsQL = Pediatric Quality of Life Inventory; RADS = Reynolds Adolescent Depression Scale; RR = relative risk; RSQ = Responses to Stress Questionnaire; SCARED = Screen for Child Anxiety Related Emotional Disorders; SCAS = Spence Children's Anxiety Scale; SCL = Skin Conductance Level; SDQ = Strengths and Difficulties Questionnaire; SEADS = Supplemental Evidence and Data for Systematic review; SLSS = Students' Life Satisfaction Scale; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SOE = strength of evidence; SSIS = Social Skills Improvement System; SSRI = selective serotonin reuptake inhibitor; SWLS = Satisfaction with Life Scale; TCA = tricyclic antidepressant; TIDieR = Template for Intervention Description and Replication; VABS = Vineland Adaptive Behavior Scales; WIAT = Wechsler Individual Achievement Test; WISC = Wechsler Intelligence Scale for Children.

VII. Summary of Protocol Amendments

Table 1. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
September 25, 2024	Literature search dates	The original protocol specified that the search would begin from the year 2010.	The revised protocol adjusted the starting date of the search to the year 2009.	Adjusting the search start date to 2009 in the revised protocol aligns with our partners' initial expectations and may result in a larger body of relevant evidence.

VIII. Previous Versions of the Protocol

- Version 1, June 26, 2024
- Version 2, September 25, 2024

IX. Key Informants

Key Informants are the end-users of research; they can include 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 the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the 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. They 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 $5,000 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 AHRQ Task Order Officer (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. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts.

Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither 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.

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

XI. Peer Reviewers

Peer reviewers will be invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC will consider all peer review comments on the draft report in preparing 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 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can 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. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XIII. Role of the Funder

This project was funded under Contract No. 75Q80120D00006/75Q80124F32019 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to 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 either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol was registered in the international prospective register of systematic reviews (PROSPERO) CRD42024539526.