Evidence-based Practice Center Systematic Review Protocol

Project Title: *Diagnosis and Management of Obsessive Compulsive Disorders in Children*

I. Background and Purpose of the Systematic Review

Background

Obsessive-compulsive disorder (OCD) is a common, chronic, and impairing psychiatric disorder, defined by one or both of two cardinal features—obsessions and compulsions. Obsessions are persistent thoughts, urges, or images that are experienced as intrusive and unwanted, generally related to one or more domains that can range from fear of illness or death to uncomfortable experiences of incompleteness or disgust. People with OCD exhibit heterogeneous compulsive rituals, avoidance behaviors, and other strategies to neutralize or avoid distress and obsessional triggers.[1] About 3% of youth (children and adolescents) experience OCD.[2] An international study of patients with OCD reported that 21% had symptom onset in childhood (≤12 years) and 36% had symptom onset during adolescence (13-17 years).[3]

Early identification and treatment of OCD is important in preventing a cascade of developmental disruptions lasting into adulthood that can affect both function and quality of life, particularly in academic and social functioning.[4-6] Untreated OCD is associated with depression, substance abuse, suicide attempts, and functional impairment in adulthood.[5, 7-10] Establishing an OCD diagnosis can be more challenging in children than in adults due to overlap with developmentally typical childhood fears and rituals, and, especially in young children, developmentally limited cognitive ability to describe their experiences.[1, 11, 12] Furthermore, OCD in children is often comorbid with depression, anxiety disorders, attention deficit hyperactivity disorder (ADHD), and eating disorders.[13] Individuals with OCD may exhibit behaviors similar to those seen in autism, tic disorders, and other anxiety-related disorders, making differential diagnosis challenging.[12]

The 2012 American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter recommends that for children and adolescents undergoing psychiatric assessment for any condition, 1. “The psychiatric assessment … should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors,” , even when not part of the presenting complaint, and 2. “If screening suggests [obsessive compulsive] symptoms may be present, clinicians should fully evaluate the child using [DSM] criteria and scalar assessment”; 3. Clinicians should use information from all available sources, and 4 “A complete psychiatric evaluation should be performed, … with attention to commonly occurring comorbid psychiatric disorders”.[1]

The reference standard for an OCD diagnosis is a clinical interview by an expert assessing current DSM criteria, often augmented, particularly in research settings, with a semi-structed diagnostic interview (e.g., the Anxiety Disorders Interview Schedule for DSM-IV-child version [ADIS-C]).[14]

Because primary care practitioners do not have the expertise or the time to do the full diagnostic interview required for diagnosis, they only identify about 10% of cases of childhood OCD.[15] Experts in assessing OCD are often overbooked, leading to potential late diagnosis or missed diagnosis of OCD in children. Brief assessment tools that accurately identify OCD (compared to reference standard methods), could allow primary care providers to make a provisional diagnosis, which would be confirmed by a specialist.[16, 17]

In terms of treatment, the 2012 AACAP Practice Parameter recommends cognitive behavioral therapy (CBT) that incorporates exposure and response prevention (ERP) as a first-line treatment for mild-to-moderate OCD in youth.[1] For moderate-to-severe OCD, the Practice Parameter recommends the addition of pharmacological treatment with a selective serotonin reuptake inhibitor (SSRI). However, questions remain about what (combinations of) treatment strategies work best for specific populations and settings. For example, individual versus family-focused versus parent-mediated, residential versus outpatient settings, through telemedicine as compared to self-guided CBT with ERP, and CBT with ERP combined with medications or other augmentations (e.g., transcranial magnetic stimulation, mindfulness), and medication alone. In addition, new treatment modalities, such as neuromodulation and complementary interventions, have come into use since the 2012 Practice Parameter.

The concept of an "autoimmune OCD" subtype has been proposed for a small subgroup of OCD patients, including pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS).[18, 19] In one study of consecutive patients presenting to a subspeciality pediatric OCD clinic, 7 of 136 (5.1%) children with OCD met proposed diagnostic criteria for PANS/PANDAS.[20] A 2018 review noted that "the concept of PANDAS brings great challenges to clinicians, patients and their families, with respect to diagnosis and treatment."[21] While a systematic review of the evidence relating to the diagnosis criteria for and specific treatment of PANS/PANDAS is outside the scope of this review, given that OCD symptoms are central components of proposed PANS/PANDAS diagnostic criteria, we will summarize the available evidence regarding the comparative effects of behavioral and pharmacological treatments for OCD in this subgroup in the report.

Recent OCD research has examined 1. Extending or improving upon the efficacy of treatments (e.g., optimization and augmentation strategies), 2. "Transporting" treatment efficacy to populations previously excluded from efficacy trials, such as younger children, individuals with autism spectrum disorder, and underserved populations, and 3. Tailoring treatment to specific subgroups (e.g., non-responders, high-conflict families).[22]

Purpose of the Review

This comparative effectiveness review will inform a planned update of the 2012 AACAP Practice Parameter.[1]

AACAP nominated this topic to the Patient-Centered Outcomes Research Institute (PCORI), which contracted with the Agency for Healthcare Research and Quality (AHRQ) to conduct the review.

Specifically, the systematic review will summarize the findings from 1. Studies related to the accuracy of assessment tools compared to reference standard methods to identify OCD in symptomatic youth and 2. Studies of psychological and/or pharmacological treatments of OCD.

The intended audience includes guideline developers, child psychiatrists and psychologists, pediatricians, family physicians, advanced practice providers, parents, and patients.

II. Key Questions and Eligibility Criteria

Key Questions (KQ)

Introduction: We facilitated a series of calls with Technical Expert Panel (TEP) members to refine the Key Questions and specific inclusion/exclusion criteria. The TEP members endorsed the clinical interview by an expert using current DSM criteria as the sole basis (reference standard) for a diagnosis of OCD. The TEP emphasized the importance of differential diagnosis and identification of comorbid conditions. Thus, rather than focusing on comparison of diagnostic strategies, KQ 1 was amended to focus on the accuracy of available assessment tools (often brief, potentially with multiple informants, such as parent or patient) in symptomatic youth for whom OCD was in the differential diagnosis. The TEP described the potential harms related to the diagnosis of OCD as being largely related to missed diagnosis or overdiagnosis. Therefore, a separate sub-question related to the harms of testing was removed. The importance of both family and social factors were mentioned by the TEP and were added as possible effect modifiers to both KQs. The TEP members agreed that the diagnosis of PANS/PANDAS is an important consideration as a potential effect modifier, but that the review should not specifically address diagnosis or treatment of PANS/PANDAS; rather, the review should maintain its focus on youth with symptoms suggestive of OCD (for KQ 1) or with an OCD diagnosis (for KQ 2).

KQ 1: How accurate are assessment tools compared to reference standard methods to identify OCD in symptomatic children and adolescents?

> **KQ 1a**: How does diagnostic accuracy of assessment tools vary by patient, family, social, or other characteristics, or by respondent type?

KQ 2: What are the comparative effects and harms of treatment interventions, used alone or in combination, for OCD in children and adolescents?

> **KQ 2a** How do the effectiveness and harms vary with patient, family, social, or other characteristics?

Study Eligibility Criteria

	Key Question 1 (Diagnosis of OCD)	Key Question 2 (Treatment of OCD)
Population	Children and adolescents (<21 years) • in whom there is clinical consideration of OCD • diagnosed with OCD and/or other conditions which may be either be comorbid with OCD or may present with similar symptoms *Include*: • Studies evaluating only children and adolescents with OCD (to estimate test sensitivity alone) *Exclude*: • Studies that include both adults and children that do not explicitly report a pediatric or adolescent subgroup in the abstract • Studies that perform population-based screening (among individuals without a clinical concern for OCD)	Children and adolescents (<21 years) with diagnosed OCD, including those with: • possible PANS/PANDAS (with OCD) • other comorbid conditions (e.g., autism) *Exclude:* • Children and adolescents diagnosed with other OCD-spectrum conditions (e.g., body dysmorphic disorder, body focused repetitive behaviors) without an OCD diagnosis • Subclinical OCD or obsessive or compulsive symptoms without an OCD diagnosis • Studies that include both adults and children that do not explicitly report a subgroup by age in the abstract

Interventions	Index Test(s)
	• Tools to diagnose OCD in symptomatic patients. For example,
	  ○ Obsessive Compulsive Inventory-Child Version (OCI-CV-R)
	  ○ Toronto Obsessive-Compulsive Scale (TOCS)
	  ○ Short Obsessive-Compulsive Screener (SOCS)
	• Diagnostic prediction models
	• Must report use of specific cut-point(s) to classify an individual as having OCD or a prediction algorithm or model to predict the probability of OCD
	• Alternative administration (e.g., child versus parent versus teacher report, in-person versus telehealth)
	
	Exclude:
	• Specific individual symptoms, behaviors, or characteristics
	• Genetic studies
		Psychological interventions for OCD, alone or in combination with pharmacological and/or other interventions, including:
		• Cognitive behavioral therapy (CBT)
		  ○ Exposure and response prevention (ERP)
		  ○ Psychoeducation
		  ○ Coping skills
		  ○ Cognitive therapy
		• Acceptance and commitment therapy (ACT)
		• Targeted family interventions
		• Other psychological interventions
		• Delivery method
		  ○ Therapist led, e.g., scheduled, in-person, or via telephone, video conference
		  ○ Self-guided, e.g., asynchronous, therapist serves as supportive coach
		
		Pharmacological interventions, alone or in combination with psychological interventions
		• Selective serotonin reuptake inhibitors (SSRIs)

	Key Question 1 (Diagnosis of OCD)	Key Question 2 (Treatment of OCD)

	• Biomarker studies	• Tricyclic antidepressants (TCA), including clomipramine
		• Serotonin and norepinephrine reuptake inhibitors (SNRIs)
		• Medication augmentation strategies
		  ○ SSRI augmentation with clomipramine, and other medications, including neuroleptics, nonsteroidal anti-inflammatory drugs (NSAIDs)
		  ○ Glutamate modulating agents (e.g., D—cycloserine, riluzole)
		• Other pharmacologic interventions, alone or in combination with psychological and/or other interventions, including dose escalation, longer treatment duration
		
		Neuromodulation interventions:
		• Transcranial magnetic stimulation (TMS),
		• Transcranial direct current stimulation (tDCS),
		• Transcranial alternating current stimulation (tACS),
		• Deep brain stimulation (DBS)
		
		Complementary/integrative therapies:
		• Naturopathic interventions
		• Mind-body practices (e.g., mindfulness, meditation, yoga)
		• Sensory integration (e.g., deep pressure)
		
		Exclude:
		  • Specific treatments for PANS/PANDAS (e.g., antibiotics, immunomodulation, intravenous immunoglobulin)

Comparators	Reference standard(s)
	• Clinical interview
	• Validated diagnostic assessment instruments (others may be included)
	  ○ Anxiety Disorders Interview Schedule for DSM-5 child version
	  ○ (ADIS-C)
	  ○ Kiddie Schedule for Affective Disorders and Schizophrenia,
		• No treatment (e.g., waitlist control)
		• Pill placebo or sham control
		• Another active intervention or co-intervention (e.g., relaxation therapy)
		• Alternative delivery methods

	Key Question 1 (Diagnosis of OCD)	Key Question 2 (Treatment of OCD)
	Present and Lifetime version (K-SADS-PL) for DSM-5 ○ Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) ○ Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) ○ Children's Yale-Brown Obsessive-Compulsive Scale Second Edition (CY-BOCS-II) • Different index tests (if also compared with reference standard) • Different reference standards (i.e., comparison of reference standards) • Different respondents (e.g., clinician, self, parent, educator) • Different methods to give test (e.g., in person vs. via tele-health) • Different populations (see effect modifiers below)	
Outcomes (prioritized outcomes have an asterisk and are in bold font)	OCD diagnosis • **Sensitivity/Specificity*** • Positive and negative likelihood ratios • Accuracy • Area under the Receiver Operator Characteristic Curve (AUC ROC) • Predicted probability of OCD (model calibration/discrimination) • Time to initiation of treatment (cohort studies) *Exclude:* • Studies not reporting predictive validity that report other psychometric properties of scales: for example, reliability or validity (content, construct, convergent, discriminant, divergent, face)	OCD symptom severity • **Children's Yale-Brown Obsessive Compulsive Scale Total (CY-BOCS)*** • **Clinical Global Impression–Severity (CGI–S)*** Treatment response and remission • **Clinical remission (posttreatment CY-BOCS total score ≤ 12 as defined by Farhat et. al.[23], or as reported)*** • **Clinical Global Impression–Improvement (CGI–I)*** Functional impairment in school, social, and home/family domains • **The Child Obsessive Compulsive Impact Scale— Revised (COIS-R)*** ○ Raters: child (COIS-C), parent (COIS-P) Family accommodation • **Family Accommodation Scale (FAS)***

	Key Question 1 (Diagnosis of OCD)	Key Question 2 (Treatment of OCD)
		Family functioning • OCD Family Functioning Scale • Family Environment Scale (FES) • Parental Attitudes and Behaviors Scale (PABS) Patient/parent reported experience measures (PREMs) Patient reported outcome measure (PROMs) • Top Problems assessment (TPA) **Quality of Life (QoL) General and Health Related (HRQoL) (validated scales only)*** • Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (QLESQ) **Acceptability of treatment*** • Parental satisfaction with services • Withdrawals/discontinuation Sleep-related problems Suicidal thoughts and behavior • Columbia Suicide Severity Rating Scale Recent Self-Report Screener (C-SSRS) Anxiety and depression **Adverse events related to treatment*** *Exclude:* • Neuroimaging (e.g., functional MRI)
Potential Effect Modifiers/Subgroups of interest	• Patient, family, social, and other characteristics, including: ○ Race/Ethnicity (racial and ethnic discrimination is the effect modifier of interest but many/most studies will not contain that so we will use race/ethnicity as a marker for likelihood of experience with discrimination and would explicitly discuss this in the review) ○ Identity and Culture (e.g., spiritual and religious beliefs and practices, native	• Patient, family, social, and other characteristics, including: ○ Race/Ethnicity (racial and ethnic discrimination is the effect modifier of interest but many/most studies will not contain that so we will use race/ethnicity as a marker for likelihood of experience with discrimination and would explicitly discuss this in the review) ○ Identity and culture (e.g., spiritual, and religious beliefs and practices, native

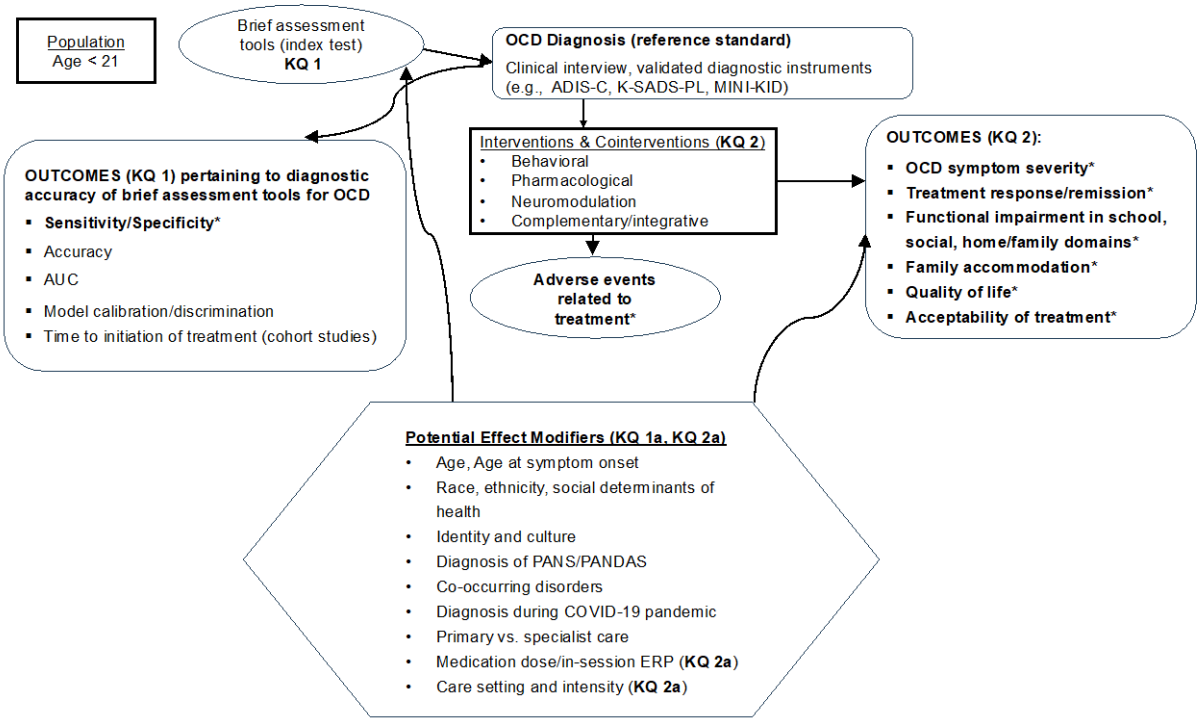
	Key Question 1 (Diagnosis of OCD)	Key Question 2 (Treatment of OCD)
	language, gender identity, sexual orientation, physical/mental disability status) ○ Age ○ Age at symptom onset ○ Social determinants of health, including education level, socioeconomic status, immigration status, refugee status, and geography (e.g., urban vs. rural) ○ Diagnosis of PANS/PANDAS ○ OCD in first degree relatives ○ Level of family accommodation ○ Co-occurring disorders (e.g., major depressive disorder, anxiety disorders, attention-deficit hyperactivity disorder, conduct disorders, autism spectrum disorder, and Tourette syndrome, other tic disorders) ○ Diagnosis during COVID-19 pandemic (as defined by study authors) ○ Primary versus specialist care • Respondent type *Exclude*: • Neuroimaging, e.g., functional MRI	language, gender identity, sexual orientation, physical/mental disability status) ○ Age ○ Age at symptom onset ○ Social determinants of health, including education level, socioeconomic status, immigration status, refugee status, and geography (e.g., urban vs. rural) ○ Diagnosis of PANS/PANDAS ○ OCD in first degree relatives ○ Level of family accommodation ○ Co-occurring disorders (e.g., major depressive disorder, anxiety disorders, attention-deficit hyperactivity disorder, conduct disorders, autism spectrum disorder, and Tourette syndrome, other tic disorders) ○ Diagnosis during COVID-19 pandemic (as defined by study authors) ○ Duration of symptoms prior to treatment ○ Symptom severity ○ In-session exposure and response prevention ○ Medication dose ○ Care settings and care intensities ▪ Traditional outpatient ▪ Intensive outpatient • Day programs (e.g., partial hospitalization) • Residential ▪ Inpatient ▪ Other care settings, including school-based settings ▪ Telehealth (vs. in-person) ▪ Primary versus specialist care
Design	Cohort or cross-sectional studies • comparing an index test(s) to a reference standard • comparing an index test(s) in two or more subgroups of interest • comparing two or more diagnostic strategies Randomized controlled trials	Comparative trials • Randomized controlled trials • Nonrandomized comparative studies ○ prospective or retrospective with appropriate adjustment for confounding Single arm studies, N ≥50

	Key Question 1 (Diagnosis of OCD)	Key Question 2 (Treatment of OCD)
	Nonrandomized comparative studies • prospective or retrospective with appropriate adjustment for confounding Systematic reviews (for reference lists only) *Exclude:* • Prevalence studies • Qualitative studies • Case reports and case series, • Unpublished studies, including conference abstracts (but include studies with reported results in the ClinicalTrials.gov database)	• with multivariable analyses of potential effect modifiers/subgroups of interest Systematic reviews (for reference lists only) *Exclude:* • Cross-sectional studies (no longitudinal follow-up) • Qualitative studies • Case reports and case series, • Unpublished studies, including conference abstracts (but include studies with reported results in the ClinicalTrials.gov database)
Timing	Any	Any
Setting	Any, including administration of test(s) in-person or via tele-health	Any

* Prioritized outcome

III. Logic Model

Figure 1. Analytic framework for Diagnosis and Management of Obsessive Compulsive Disorders in Children



Abbreviations: ADIS-C = Anxiety Disorders Interview Schedule for DSM-5, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version , MINI-KID = Mini-International Neuropsychiatric Interview for Children and Adolescents, AUC = Area under the receiver operating characteristic curve, KQ = Key question, OCD = Obsessive-compulsive disorder, PANS = pediatric acute-onset neuropsychiatric syndrome, PANDAS = pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections

IV. Methods

The systematic review for KQs 1 and 2 will follow the Evidence-based Practice Center Program methodology, as described in its Methods Guide, particularly as it pertains to reviews of comparative effectiveness.[24]

Criteria for Inclusion/Exclusion of Studies in the Systematic Review: See detailed eligibility criteria in Section II.

In brief, for Key Question 1, we will include studies that evaluate the diagnostic accuracy (predictive validity) of different assessment scales for OCD in children and adolescents, compared to a reference standard (clinical interview by an expert assessing current DSM criteria, possibly augmented by a semi-structured interview using a validated diagnostic assessment instrument). We will evaluate outcomes as listed in the *Study Eligibility Criteria* section, focusing on sensitivity and specificity jointly.

For Key Question 2, we will include studies comparing psychological and pharmacological interventions for OCD, alone or in combination, compared to no treatment, placebo or another

active intervention or co-intervention(s), or delivery method. We will evaluate outcomes as listed in the *Study Eligibility Criteria* section, focusing on listed prioritized outcomes related to OCD symptom severity, treatment response and remission, functional impairment, family accommodation, quality of life, and acceptability of treatment and adverse events related to treatment. Prioritized outcomes are in bold font (with asterisks) in the Study Eligibility Criteria table.

For all Key Questions, we will attempt to identify predictors and moderators of treatment effect (see potential effect modifiers/subgroups of interest).

With input from the TEP, we have prioritized the following list of outcomes. As described below, we will evaluate the strength of evidence (SoE) for these outcomes. We may also evaluate SoE for other included outcomes. The prioritized outcomes include:

KQ 1

- Sensitivity/Specificity

KQ 2

- OCD symptom severity
- Treatment response and remission
- Functional impairment in school, social, and home/family domains
- Family accommodation
- Quality of life
- Acceptability of treatment
- Adverse events related to treatment

Literature Search Strategies to Identify Relevant Studies to Answer the Key Questions

We will search for studies and existing systematic reviews in MEDLINE (via PubMed), the Cochrane Register of Clinical Trials, the Cochrane Database of Systematic Reviews, Embase, CINAHL and PsycINFO and Education Resources Information Center (ERIC) databases. We will search index terms, along with free-text words, for concepts related to OCD and pediatric and adolescent populations. Duplicate citations will be removed prior to screening. We will not apply language, date, or country restrictions. Search strategies will include filters to remove nonhuman studies and articles that are not primary studies or systematic reviews. The PubMed search strategy is detailed in Appendix A.

Additional searches will be conducted in the ClinicalTrials.gov registry for ongoing and unpublished studies with study results. The reference lists of relevant existing systematic reviews will be screened for additional eligible studies. A Supplemental Evidence And Data for Systematic review (SEADS) portal and Federal Register Notice will be available for this review. We will ask the TEP to provide citations of potentially relevant articles and will screen any additional citations identified by the TEP and other experts and stakeholders during peer and public review. Additional articles suggested to us from any source, including peer and public review, will be screened with the same eligibility criteria as the studies identified in the database searches.

Per our EPC's standard processes, we will take advantage of the machine learning capacities of Abstrackr (http://abstrackr.cebm.brown.edu/) to limit resources spent on abstract screening. We will train the machine learning algorithm as follows: (1) We will review the reference lists from known existing systematic reviews and clinical practice guidelines to identify potentially

relevant studies for each KQ. (2) We will confirm this set of potentially relevant citations was successfully captured by our PubMed search. (3) Based on recently published work by Sampson et. al.,[25] we will select the top 500 articles from our search using PubMed's best-match algorithm. (4) The articles from steps (1) and (3) will be entered into Abstrackr and screened by all team members, with resolution of all conflicts in conference. (5) Subsequently, citations found by the full literature searches will be added to the already-screened citations in Abstrackr, and abstract screening will continue in duplicate, with conflicts adjudicated in conference or by a third screener. (6) As screening progresses, the pretrained Abstrackr machine learning algorithm will continue to adapt and will sort the list of unscreened abstracts such that the most potentially relevant articles are presented first. This process will make screening more efficient and will enable us to capture the preponderance of relevant articles relatively early in the abstract screening process. (7) We will stop double screening when the predicted likelihood of the remaining unscreened papers being relevant is very low. We typically use a threshold for the prediction score of the unscreened citations of 0.40 (this threshold is based on experience with several dozen screening projects and an analysis in preparation for publication but may be lowered depending on whether we continue to find eligible abstracts near the threshold). To confirm that the selected prediction score threshold is appropriate for this literature base, when the maximum prediction score is <0.40, we will screen at least 400 additional consecutive citations (this sample size is chosen because the upper 97.5% confidence interval bound for a proportion of 0/400 is less than 1%). If any of the 400 citations are screened in (at the abstract level), we will repeat the process (restart counting an additional 400 citations) until we have rejected at least 400 consecutive citations.

Potentially relevant citations will be retrieved in full text. Non-English language articles will be screened, and data extracted from full text, either by readers of the relevant languages or after translation via Google Translate (https://translate.google.com/), if possible. The search strategies for all databases will be peer reviewed by another experienced systematic review librarian. Searches will be updated during the draft report's public posting period.

Evidence Map

Due to time and resource restrictions, for KQ 2 we plan to restrict synthesis within the full report to comparisons with three or more studies (with some possible exceptions, described below). Our logic is that these are the comparisons researchers have deemed to be of greatest interest and they are the comparisons we are most likely to be able to make conclusions about (beyond "insufficient evidence"). The restriction will reduce the need to spend resources on extracting and summarizing studies that will only lead to "insufficient" evidence. However, if we find comparisons with two studies, both of which are large (N≥100) and neither of which is at high risk of bias, we will include these in the full report. All treatment comparisons that meet criteria, regardless of number of studies, will be included in the appendix as an "evidence map" spreadsheet. The evidence map will provide a high-level overview of the evidence, includingbasic study design, size, population, intervention, and high-level effectiveness information. We will include the extractions for this spreadsheet to SRDRplus to allow it to be easily downloadable and searchable.

Data Extraction and Data Management

Data from eligible studies will be extracted into the Systematic Review Data Repository Plus (SRDR+) software. Each article will be extracted by one researcher and entered data will be confirmed by a second researcher. Individual studies with multiple publications will be extracted

as a single study (with a single entry in SRDR+). Articles that report multiple studies will be entered into SRDR+ separately for each study.

For each study, we will extract publication data, study design features, population characteristics, intervention and comparator names and descriptions, relevant outcomes and their definitions, and funding source. All subgroup analyses or other evaluations of heterogeneity of treatment effect will be extracted.

Assessment of Quality and/or Methodological Risk of Bias of Individual Studies

We will evaluate each study for risk of bias and methodological quality during data extraction. Each study will be assessed by one researcher. Their assessments will be confirmed by a second researcher. Disagreements will be discussed in conference with the team or with the Lead.

For randomized controlled trials (RCTs), including cluster randomized trials, we will complete the Cochrane Risk of Bias tool,[26] which addresses issues related to randomization and allocation concealment; blinding; deviations from intended intervention; missing data; outcome measurement; and reporting biases. We will also evaluate the adequacy of descriptions of study participants, interventions, outcomes, and study designs. In addition, we will assess the adequacy of analyses. Questions related to outcome assessor blinding, missing data, outcome measurement reporting adequacy, and analytic adequacy will be assessed for each outcome.

For nonrandomized comparative studies, we will add assessments of specific elements from ROBINS-I[27] related to selection bias (comparability of groups) and relevant concepts addressed for RCTs (i.e., related to missing data, outcome measurement, analysis plan).[27] The questions will be assessed for each outcome (e.g., whether each outcome was adjusted for potential confounders).

For single arm studies, we assessed methodological quality using items from the Cochrane Risk of Bias Tool[26] that pertain to participant loss to follow up, incomplete outcome data, and selective outcome reporting, and items from the National Heart, Lung, and Blood Institute (NHLBI) Tool[28] that focus on the adequacy of descriptions of eligibility criteria, interventions, and outcomes. Treatment effect estimates from single arm trials will not be used to inform graded conclusions. We may use single arm trials to provide context for graded conclusions regarding applicability and feasibility of specific interventions or in specific populations. If available, we will extract and summarize evidence regarding predictors of within-arm treatment effects.

For single test diagnostic accuracy studies, we will assess specific elements from the QUADAS-2, and if needed, the QUADAS-C, for comparative diagnostic accuracy studies.[29-31]

Data Synthesis

We will summarize the evidence both narratively and, when feasible, quantitatively.

Each study will be described in summary and evidence tables presenting study design features, study participant characteristics, descriptions of interventions, outcome results, and risk of bias/methodological quality. In text and tables, we will describe the characteristics of the study participants (particularly including those related to subgroups of interest) and features of the interventions (particularly including those related to regimen details). In extraction and summary of RCTs and NRCSs, we will preferentially include adjusted over crude analyses.

The specific metrics (summary effect measures) to be meta-analyzed will depend on available, reported study data. We will prefer continuous effect metrics on the original scale, rather than use standardized effect sizes, but may consider standardized effect sizes if necessary to allow comparisons across studies. Continuous metrics will be preferred over categorical

metrics. If reported or estimable, we will analyze net mean differences (NMD; the difference between arms of the within-arm changes in outcome). Where appropriate or necessary, we will analyze mean differences between groups.

For diagnostic test studies, we will extract all relevant outcome measures (e.g., sensitivity, specificity, AUC ROC). If reported, we will extract relevant measures at all reported thresholds.

Where appropriate and feasible, we will conduct random-effects meta-analyses of comparative studies if at least three studies are sufficiently similar in population, interventions, outcomes, and study design. For KQ 1, we will attempt to create summary ROC curves. For KQ 2, we will explore the possibility of conducting network meta-analyses of a widely reported outcome (e.g., CY-BOCS) to indirectly compare alternative treatment regimens across studies.

As feasible, we will describe reporting of differences in effects and harms by different factors, subgroups, or predictors. We expect to primarily rely on reported within-study differences in effects (or harms). However, we will look for opportunities to qualitatively and/or quantitatively summarize and/or compare results across studies.

Grading the Strength of Evidence for Prioritized Outcomes

Following AHRQ Methods guidance[23] the review team will consider the number of studies, their designs, limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies, and will assign a consensus strength of evidence (SoE) rating of high, moderate, low, or insufficient to estimate an effect, addressing each prioritized outcome for each Key Question.

Outcomes with highly imprecise estimates (with 95% confidence intervals that extend beyond both 0.5 and 2.0 for categorical outcomes), highly inconsistent findings across studies (in terms of directions of effect), or with data from only one study were deemed to have insufficient evidence to allow for a conclusion (with the exception that a single particularly large, well-conducted, and generalizable single study could provide low SoE). This approach is consistent with the concept that for imprecise evidence "any estimate of effect is very uncertain," which is the definition of Very low-quality evidence per the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[32]

Assessing Applicability

For each Key Question, we will describe the applicability of the included studies primarily based on the studies' eligibility criteria and their included participants. We will describe the populations to which the evidence may be most applicable and will highlight populations for whom the evidence may be less applicable.

V. References

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VI. Definition of Terms and Abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
ACT	Acceptance and Commitment Therapy
ADIS-C	Anxiety and Related Disorders Interview Schedule-child version
ADHD	Attention-deficit hyperactivity disorder
AHRQ	Agency for Healthcare Research and Quality
AUC	Area under the curve
CALIS	Children’s Anxiety Life Interference Scale
CBT	Cognitive behavioral therapy
CGAS	Children’s Global Assessment Scale
CGI	Clinical Global Impression-Improvement Scale

CHOCI	Children's Obsessional Compulsive Inventory
COIS	The Child Obsessive Compulsive Impact Scale
C-SSRS	Columbia Suicide Severity Rating Scale Recent Self-Report Screener
CY-BOCC	Children's Yale-Brown Obsessive-Compulsive Scale
DBS	Deep brain stimulation
ERP	Exposure and response prevention
HRQoL	Health related quality of life
KI	Key Informant
KQ	Key Question
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version
MeSH	Medical subject heading
MINI-KID	Mini-International Neuropsychiatric Interview for Children and Adolescents
fMRI	Functional magnetic resonance imaging
NRCS	Nonrandomized comparative study
NSAID	Nonsteroidal anti-inflammatory drug
OCD	Obsessive-compulsive disorder
OCI-CV-R	Obsessive Compulsive Inventory —Child Version revised
PANS	Pediatric acute-onset neuropsychiatric syndrome
PANDAS	Pediatric autoimmune neuropsychiatric disorder associated with streptococcus
PABS	Parental Attitudes and Behaviors Scale
PCORI	Patient-Centered Outcomes Research Institute
PICODTS	Population, Intervention, Comparator, Outcome, Design, Timing, and Setting details for systematic review search
PREM	Patient-reported experience measure (that reflects the impact of the process of care on the patient's experience)
PROM	Patient-reported outcome measure (that reflects patient perceptions of their health status)
QLESQ	Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form
QoL	Quality of life
RCT	Randomized controlled trial
RCADS-25	Revised Children's Anxiety and Depression Scale
ROC	Receiver operator characteristic curve
SEADS	Supplemental Evidence And Data for Systematic Review
SNRI	Serotonin and norepinephrine reuptake inhibitors
SOCS	Short Obsessive-Compulsive Screener
SSRI	Selective serotonin reuptake inhibitors
SoE	Strength of evidence
SRDR+	Systematic Review Data Repository Plus
TCA	Tricyclic antidepressants
TEP	Technical expert panel
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TOCS	Toronto Obsessive-Compulsive Scale

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe each change and give the rationale in this section.

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing the public comments and seeking input from Key Informants (KIs).

IX. Key Informants (KIs)

KIs are end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with a role in making health care decisions. Within the EPC program, the KIs' role is to provide input into refining the Key Questions for research that will inform healthcare decisions. The EPC solicits input from KIs when refining questions for systematic review. KIs 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.

KIs must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Drawing upon their roles as end-users, diverse individuals are invited to serve as KIs. Those who present with potential conflicts can be retained although the TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Expert Panel (TEP)

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes. 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 the completion of a thoughtful, relevant systematic review. As such, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts.

Technical Experts provide further input to finalize the KQs, study eligibility criteria, and analysis plans. The Technical Experts provide feedback on the full protocol. They provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. They may help to identify particular studies or databases to search for studies to be included in the review. 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 although the AHRQ 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 $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

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 from participation in the review.

XIII. Role of the Funder

This project is funded by the Patient-Centered Outcomes Research Institute (PCORI) and executed under AHRQ, U.S. Department of Health and Human Services through Contract Nos. 75Q80120D00001/75Q80123F32010 (Task Order #10). The TOO will review contract deliverables for adherence to contract requirements and quality. The authors of this report will be responsible for its content. Statements in the report should not be construed as endorsement by PCORI, AHRQ, 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).

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