Evidence-based Practice Center Systematic Review Protocol

Project Title: *Management of Suicidal Thoughts and Behaviors in Youth*

I. Background and Objectives for the Systematic Review

Suicide is a leading cause of death in young people and an escalating public health crisis. Suicidal thoughts and behaviors most commonly emerge during the transition from childhood into early adolescence, with the first suicide attempts typically occurring and peaking in mid-adolescence before decreasing with the transition into young adulthood.[1, 2] In the United States, mortality rates associated with suicide have steadily increased since 2007. Over a similar time period, suicide-related emergency department visits for youth aged 5–24 years in the United States have risen from 0.9% to 4.2%, with an average annual increase of 23.1%.[3, 4] A study of suicide decedents aged 5–11 years in the United States showed that 9% of the cases were in the 5–9 years age group,[5] and male children had a higher suicide rate than female children.[6]

Despite the alarming increase in suicidal thoughts, behaviors, and completed suicides among young people, there are few evidence-based guidelines to inform the implementation of interventions for children, adolescents, and young adults at high risk for suicidal thoughts and behaviors.[7, 8] In practice, treatments for suicidal thoughts and behaviors typically include psychosocial and pharmacological interventions or their combination.[8] Yet, the effectiveness of these treatment options on children and adolescents at risk for suicidal thoughts and behaviors is unclear. The majority of the available studies have examined psychosocial interventions to reduce suicidal outcomes in youth, and a considerably smaller number of studies have examined the effectiveness of medications in children and adolescents, mostly to manage suicidal symptoms and the sequalae of other mental health disorders. Evidence regarding the combination of psychosocial and pharmacological interventions to address suicidal thoughts and behaviors in youth is even more scarce.[8, 9] Given the profound need to address the current suicide crisis, other interventions have been proposed in this context, including electroconvulsive therapy, brain stimulation interventions, and other neurotherapeutics.[9, 10]

Psychosocial Interventions

A wide variety of psychosocial interventions have been developed for reducing suicidal thoughts and behaviors in young people. The delivery of these interventions has been studied in various contexts including inpatient hospitalization, intensive outpatient treatment programs, outpatient appointments, telemedicine visits, or via digital platforms such as websites, apps, and wearables. Broadly, psychosocial interventions provide some combination of support, skill development, problem solving, emotion regulation and management, behavioral planning, family engagement and communication training, and practical safety planning (including limiting access to lethal means such as firearms).[8, 11-15] The specific psychosocial interventions that have been used to treat suicidal youth include cognitive behavioral therapy,[16] dialectical behavioral therapy,[15] family therapy,[17, 18] attachment-based therapies, and variations and combinations of these approaches. These interventions have diverse conceptual approaches and treatment intensities

from online modules to intensive home- and community-based interventions. There is no clear consensus on the optimal intensity or mode of delivery of these interventions. A recent meta-analysis of 30 randomized controlled trials of psychosocial interventions compared with any control treatment found that psychosocial interventions as a whole showed little effectiveness to reduce suicide risk in adolescents.[8]

Pharmacological Interventions

Research focused on pharmacological interventions for suicidal thoughts and behaviors in youth is considerably more limited than research on psychosocial treatments. While no medications have been studied specifically to reduce suicidal outcomes in youth, selective serotonin reuptake inhibitors (SSRIs) have shown effectiveness in improving symptoms of mental health disorders associated with suicide, such as major depressive disorder (MDD).[19, 20] However, meta-analyses of SSRI studies suggest a small but significant increased risk of suicidal thoughts and behaviors in adolescents, leading the U.S Food and Drug Administration to institute a black box warning for increased risk of suicidal thoughts and behaviors in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders.[21, 22] While other pharmacological agents such as selective norepinephrine reuptake inhibitors, lithium, clozapine, ketamine, esketamine, and psychedelic treatments have been suggested as potential treatments for suicidal thoughts and behaviors in young people, there is limited research about these pharmacological agents in adolescents.[9, 23-25]

Other Psychiatric Interventions

Neurotherapeutics or neuromodulatory interventions such as electroconvulsive therapy and transcranial magnetic stimulation have been studied for the treatment of suicidal thoughts and behaviors in adolescents and young adults. Existing studies have limited rigor and only a few were controlled trials.

Beyond the limited evidence base, there are other challenges in the literature describing interventions for suicidal thoughts and behaviors in children, adolescents, and young adults. Existing studies are heterogenous and typically do not study treatments for suicidal thoughts and behaviors independent of psychiatric disorders, such as MDD, bipolar disorder, and substance use disorders.[8] There are diverse outcome measures that are consistently based on subjective self-reported measures for suicidal ideation with variable validity and reliability as opposed to objective behaviors (e.g., suicide attempts). There are also considerable knowledge gaps on how to tailor interventions for high-risk groups such as youth of different sexes, sexual orientations, and gender identities, ethnic/racial minorities, or youth who have experienced homelessness, poverty, or exposure to violence. Last, knowledge translation and implementation of effective treatments are consistent challenges related, in part, to clinician shortages and lack of access to care.[26, 27] Given the challenges mentioned, we will conduct a systematic review to evaluate the totality of evidence associated with the management of suicidal thoughts and behaviors in youth.

Purpose of the Review

This systematic review will assess the effectiveness, comparative effectiveness, and harms of treatments for suicidal thoughts and behaviors in youths. If evidence is available, we will also assess how differences in effectiveness and harms are influenced by components of psychosocial treatments, and patient and environmental characteristics. This work will be used by the American Psychological Association to develop a new clinical practice guideline on this topic.

II. The Key Questions (KQs)

The key questions were posted for public comment between July 17, 2023 and August 04, 2023 We recruited eight Key Informants and five Technical Experts with different expertise and backgrounds and obtained input on the study protocol through four 1-hour video conference calls. The Key Informant calls were held on October 30, 2023 and November 20, 2023, and the Technical Expert Panel calls were held on February 23, 2024, and March 14, 2024. The public comments, Key Informants, and Technical Experts emphasized the public health implications and importance of the topic, citing the increasing trend of suicide in youth. The Technical Experts also provided critical suggestions on evaluating outcomes by the timing of occurrence and specific scales used to measure the severity of suicidal ideation. They recommended a different age categorization and advised evaluation of the scalability of interventions, citing that some treatments, such as DBT, although having evidence of efficacy, require long-term training and commitment, and thus have high dropout rates and are not easily scalable. In response, we will analyze outcomes at the end of the intervention and at the longest followup. We also added examples of scales that are commonly used to measure suicidal ideation and intent and changed the age categorization. We added an evaluation of scalability to the applicability assessment.

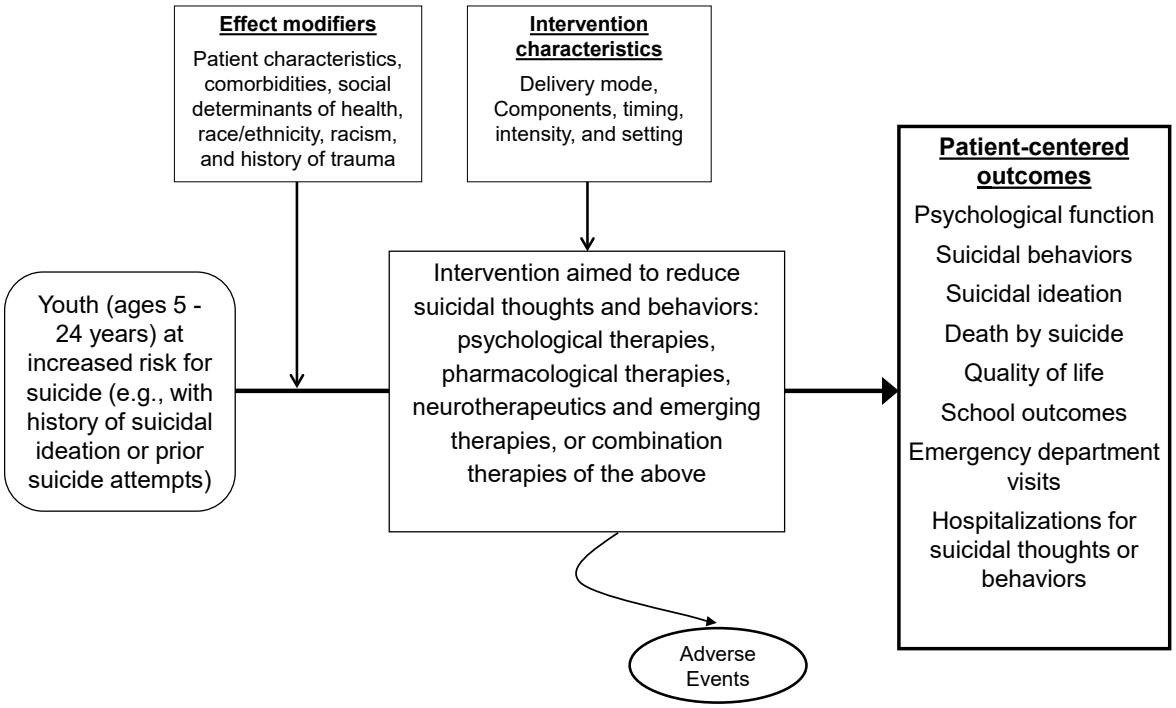
KQ 1. For youth, what are the effectiveness, comparative effectiveness, and harms of treatments for suicidal thoughts and behaviors?

a) What are the components of effective psychosocial treatments (e.g., frequency or intensity of therapy and/or aspects of the therapeutic modality)?
b) How do social determinants of health, racism and disparities, care delivery methods, patient demographics and psychiatric or developmental co-occurring conditions affect outcomes?

III. Analytic Framework

The draft analytic framework can be found in Figure 1.

Figure 1. Analytic framework



IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

We will apply the inclusion and exclusion criteria listed in Table 1 for the studies identified in the literature search. We will limit the literature search to studies published after the year 2000 as older studies may not reflect contemporary clinical practice.

Table 1. PICOTS (population, interventions, comparators, outcomes, timing, setting)

PICOTS Elements	Inclusion Criteria	Exclusion Criteria

Population	• Ages 5–24 years who have a heightened risk for suicide, including—
	  ○ Those who have suicidal ideation (i.e., thinking about or planning suicide) with or without self-injurious behaviors (i.e., suicide attempt or self-injurious behavior, including self-directed deliberate injury or potential for injury)
	  ○ Those who have made suicide attempts in the absence of known suicidal ideation
	  ○ Those who have a recent hospital discharge for mental health treatment
	  ○ Those who have shown command hallucination (i.e., auditory hallucinations that instruct a patient to act in specific manners) or intense stress/distress
	  ○ Those who are identified as having heightened risk by PHQ-9, C-SSRS, or ASQ
	  ○ Those who are from racial/ethnic minority groups known to have increased risk of suicide
	  ○ Those who are from the LGBTQ+ community
	  ○ Those who have/had exposure to high crime/violence
		• Animals
		• Adults aged >25 years

Interventions	• An intervention aimed to reduce suicidal and thoughts behaviors—
	  ○ Psychosocial interventions
	  ○ Pharmacological therapy
	  ○ Neurotherapeutics and emerging therapies
	  ○ Combination therapies of the above
		• Complementary or integrative health interventions (e.g., light therapy, supplements)

Comparators	• Treatment as usual • Another psychosocial intervention • Another pharmacological therapy • Combination therapies of the above	• None
Outcomes	• Suicidal behaviors (e.g., suicidal attempts, self-harm with suicidal intent, self-harm without suicidal intent) • Suicidal ideation • Measures of severity of suicide ideation and intent (e.g., C-SSRS, Sheehan STS, SIQ) • Deaths by suicide • Hospitalizations for suicidal thoughts or behaviors • Emergency department visits for suicidal thoughts or behaviors • Measures of psychological functioning after receiving an intervention targeting suicidal behaviors and thoughts (e.g., depression, anxiety, stress, coping, sense of purpose, agency, burdensomeness, thwarted belonging as reported by child and caregivers, quality of life • School outcomes [e.g., functioning in school, attendance, drop-out]) • Adverse events, including study withdrawals	• None
Timing	• At the end of intervention and at the end of followup	• None
Settings	• Any (e.g., outpatient, inpatient, emergency department)	• None

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Study design	• RCTs • Comparative observational studies • Before—after studies • Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	• In vitro studies • Nonoriginal studies (e.g. narrative reviews, editorials, letters, or erratum), • Cross-sectional (i.e., nonlongitudinal) studies
Subgroup analysis	• Delivery methods (e.g., telehealth, in-home treatment, school-based intervention, clinic) • Age group (5–13 years, 14–17 years, and 18–24 years) • Gender/gender identity • Race/ethnicity • History of trauma • Experience of racial/ethnic discrimination and marginalization • Sexual orientation • Co-occurring conditions (e.g., MDD, bipolar disorder, mood disorders, substance use disorders, eating disorders, posttraumatic stress disorder, autism, intellectual/developmental disabilities, other special needs), • Intervention objectives (i.e., addressing suicidal thoughts vs. suicidal behaviors; ongoing treatments following crisis care vs. crisis care) • Clinical settings (e.g., outpatient, inpatient, residential, emergency department) • Timing of outcome assessment (e.g., long-term outcome assessment, short-term outcome assessment) • Social determinants of health (e.g., access to mental healthcare, access to housing, poverty, exposure to violence/crime)	• None
Publications	• Full-text peer-reviewed studies published in English • Studies published after the year 2000	• Non-English language studies • Conference abstracts

Abbreviations: ASQ = Ask Suicide-Screening Questions; C-SSRS = Columbia Suicide Severity Rating Scale; LGBTQ+ = Lesbian Gay Bisexual Transgender Queer/Questioning Plus/Others; MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire-9; RCT = randomized controlled trial; Sheehan STS = Sheehan Suicidality Tracking Scale; SIQ = Suicidal Ideation Questionnaire

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

We plan to conduct a comprehensive database search, including Embase®, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE®, Cochrane Central Registrar of Controlled Trials, Ovid® Cochrane Database of Systematic Reviews, and Scopus® from the year 2000 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 the U.S. Food and Drug Administration, ClinicalTrials.gov, Health Canada, the U.K. Medicines and Healthcare Products Regulatory Agency, relevant conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. 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 X9; Thomson Reuters, Philadelphia, PA). In addition, a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal will be available to collect additional study-specific information from industry stakeholders, professional societies, and researchers. A Federal Register Notice will be posted for this review.

Independent reviewers, working in pairs, will screen the titles and abstracts for all citations using the prespecified 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 cannot be reached, a third reviewer will resolve the conflict. We will use a web-based systematic review software, DistillerSR® (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process.

Data Abstraction and Data Management

At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (i.e., author, year, study design, inclusion and exclusion criteria, patient characteristics, intervention, 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 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. An additional reviewer will review the data extraction and resolve conflicts. If the included studies do not report all necessary information (e.g., methods and results), we will contact authors directly. DistillerSR® will also be used to create data extraction forms and facilitate data extraction.

Assessment of the Risk of Bias of Individual Studies

We will evaluate the risk of bias of the included RCTs using the Cochrane Collaboration's Risk of Bias 2 tool[28] to assess bias from the randomization process, intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources of bias. For observational (nonrandomized) studies, we will select appropriate items from the Newcastle-Ottawa Scale.[29]

Data Synthesis

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

We will determine whether meta-analysis is appropriate (i.e., more than two studies 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 a meta-analysis is deemed appropriate, we plan to use the DerSimonian and Laird random-effects method with the Hartung-Knapp-Sidik-Jonkman variance correction to combine direct comparisons between treatments if the number of studies included in the analysis is larger than three.[30] The fixed effect method based on the Mantel and Haenszel method will be adopted when the number of studies is three or fewer. We will evaluate heterogeneity between studies using I^2 indicator. To further explore heterogeneity, we plan to conduct preplanned subgroup analyses (listed in Table 1).

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes
We will grade the strength of the body of evidence (SOE) per the Evidence-based Practice Center (EPC) Methods Guide for Comparative Effectiveness Reviews on assessing SOE.[31]

RCTs will start with a provisional high SOE grade, while observational studies will start with a provisional low SOE grade.[31] The domains to be used for determining final SOE grade will be: 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 and caregivers), consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity), and the likelihood of reporting and publication bias.

We will lower SOE grading when sensitivity analyses (1) show substantial difference in estimates derived from high or unclear risk of bias studies versus estimates derived from studies at low risk of bias or (2) when the majority of available studies (in a particular comparison) have high or unclear risk of bias. SOE grading will be also lowered when important heterogeneity is identified.

Based on this assessment and the initial study design, we will assign SOE rating as high, moderate, low, or insufficient to estimate an effect with the definitions below.

High: We are very confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable).

Moderate: We are moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable).

Low: We have limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable).

Insufficient: We are unable to estimate an effect or have no confidence in the estimate of effect.

We will produce summary of evidence tables that will provide for each comparison and for each outcome: data source, effect size, SOE rating, and rationale for judgments made on each domain of evidence rating.

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.[31] Applicability for each outcome will be summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. We will summarize the available data to present the range of PICOTS characteristics that was studied in the available literature, thus facilitating future decision making based on this body of literature. The following factors that may affect applicability include patient factors (e.g., demographic characteristics [e.g., age, race, ethnicity, socioeconomic status]), patient medical comorbidities, and intervention factors (e.g., intervention objectives, clinical settings, care delivery methods). We will assess scalability of interventions by summarizing dropout rates and any other relevant information about scalability provided in the studies. We will use this information to evaluate applicability of the evidence to

real-world clinical practice in typical U.S. settings. 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

AHRQ	Agency for Healthcare Research and Quality
ASQ	Ask Suicide-Screening Questions
C-SSRS	Columbia Suicide Severity Rating Scale
EPC	Evidence-based Practice Center
KQ	Key Question
LGBTQ+	Lesbian Gay Bisexual Transgender Queer/Questioning Plus/Others
MDD	Major Depressive Disorder
PHQ-9	Patient Health Questionnaire-9
PICOTS	Population, Interventions, Comparators, Outcomes, Timing, Setting
RCT	Randomized Controlled Trial
SEADS	Supplemental Evidence and Data for Systematic Reviews
Sheehan STS	Sheehan Suicidality Tracking Scale

SIQ	Suicidal Ideation Questionnaire
SOE	Strength of Evidence
SSRI	Selective Serotonin Reuptake Inhibitor
TEP	Technical Expert Panel
TOO	Task Order Officer
U.K.	United Kingdom
U.S.	United States

VII. Summary of Protocol Amendments

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

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 of the public comments and seeking input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the Key Questions are specific and relevant.

IX. Key Informants

Key Informants are the end-users of research; 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 multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. 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 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 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

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XIV. Registration

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