Core Outcome Set Development for Adolescent Major Depressive Disorder Clinical Trials:

A Registered Report

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COMET registration: http://www.comet-initiative.org/studies/details/1122

Facebook (87 words)
New #JAACAP registered report describes the International Network for Research Outcomes in Adolescent Depression Studies (www.IN-ROADS.org) protocol to engage youth, caregivers, clinicians, trialists, and other key stakeholders using COMET Initiative methodology to develop a #CoreOutcomeSet for use in adolescent depression clinical trials. This Core Outcome Set will be a small minimum set of meaningful outcomes recommended for measurement in all future depression trials in teens. The use of this set will ensure comparability between trials, optimize research synthesis efforts, and enhance translation of research to clinical practice. #RegisteredReports #Depression #Outcomes

Twitter (257 characters)
New #RegisteredReport in @JAACAP describes protocol for #CoreOutcomeSet development for #adolescent #depression #trials using @COMETinitiative methodology with innovative youth engagement approaches @inroadscos @drsuneetamonga @NancyJButcher www.in-roads.org

SYNOPSIS

Introduction Summary

Major Depressive Disorder (MDD), associated with life-time prevalence rates of 11% in adolescents, results in significant disease burden worldwide.[1] Adolescent MDD clinical trials evaluate interventions by measuring the effects of the interventions on various treatment outcomes, such as "severity of depressive symptoms" or "social functioning".[2] The ability to compare or contrast treatments and generate usable, meaningful data however, depends on trials using well-selected and well-defined outcomes measured by validated tools.[2,3] To ensure comparability between trials, core outcome sets (COS) have been developed for use in other healthcare areas, which has resulted in improved standardization of outcome selection and measurement across effectiveness trials, facilitating the synthesis of results in systematic reviews.[4] A COS is an agreed, standardized *minimum* set of outcomes that should be measured and reported in all clinical trials in specific areas of health, while not precluding the inclusion of other outcomes.[4] More recently, a growing awareness of the importance of COS has led to greater patient engagement in outcome selection and measurement, resulting in a stronger emphasis on quality of life and functional outcomes as being critical to evaluate.[3,5] The primary objective of this project will be to develop an evidence- and consensus-based COS for adolescent MDD clinical trials assessing any type of intervention by following COS development methodology recommendations from the Core Outcome Measures in Effectiveness Trials (COMET) Initiative.[4] Innovative adaptations to ensure engagement of youth and caregivers will be used throughout this project; thus, a secondary objective is to develop guidance for incorporating youth and family engagement in the development of COS for adolescent mental health.

Method Summary

This project is called the International Network for Research Outcomes in Adolescent Depression Studies (IN-ROADS) project and is registered with the COMET Initiative.[6] For the first stage of COS development, namely gaining agreement on "what" should be measured, we will follow the Core Outcome Set-STAndards for Development (COS-STAD)[7] and the Core Outcome Set-STAndardised Protocol Items (COS-STAP)[8] guidelines. A recently conducted scoping review of adolescent MDD randomized clinical trials identified 86 unique outcomes measured using 118 different outcome measurement instruments (OMIs), demonstrates the significant variability in outcome selection and measurement across adolescent MDD trials.[2] These results highlight the need to develop a COS for adolescent MDD trials.[2] Outcomes identified from this the scoping review will be pruned into a smaller list of generalizable outcomes using a nominal group technique resulting in the *"scoping review generated"* outcomes (Figure 1). In parallel, youth at different stages of their care pathway and caregivers will be engaged through focus groups to identify outcomes that they feel are important to measure when evaluating treatments for depression, resulting in a list of *"youth & caregiver generated"* outcomes. The two lists will be

combined and voted on in an international web-based Delphi study. A Delphi study is an iterative, multi-stage survey method that aims to yield consensus from disparate opinions by providing controlled feedback between rounds.[4,9] Use of a web-based Delphi study will allow engagement of a diverse and international group of stakeholders, inclusive of youth and caregivers as well as professionals. Delphi study participants will rate the importance and feasibility of including each outcome in a COS on a 9-point Likert scale over two survey rounds.[4] Following COMET guidelines,[4] pre-specified consensus criteria for including, removing, or adding new outcomes will be applied for each round (e.g., >70% voted of high importance or feasibility for "consensus in" the COS). A final consensus meeting will bring together youth, caregiver, and professional stakeholder input to establish a final recommended COS informed by results from the Delphi.

The second stage of COS development will determine how best to measure each outcome in the COS. Following the recommendations from COMET and the COnsensus-based Standards for the Selection of health Measurement INstruments (COSMIN),[4,10] we will: (1) systematically identify existing candidate OMIs for each COS outcome, (2) evaluate the measurement properties and feasibility aspects of the OMIs, and (3) use consensus methods to select one OMI for each COS. Youth and caregiver input will be incorporated into the OMI selection process.

Significance Summary

This project will engage international key stakeholders, including youth and caregivers, to generate a COS for adolescent MDD clinical trials that will help lead to improved outcome selection and measurement across MDD trials. Greater standardization across adolescent MDD trials will ensure comparability between trials on the key outcomes that are important to knowledge users, facilitating the translation of evidence to practice through systematic reviews and meta-analyses.

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Figure 1. Outline of core outcome set development process.

Abbreviations: COS, core outcome set.

REGISTERED REPORT

INTRODUCTION

Major Depressive Disorder (MDD) is a serious global health problem impacting over 264 million people worldwide and resulting in a significant burden of disease.[1,2] In adolescents, life-time prevalence rates are 11%, while up to 13% may experience symptoms of a major depressive episode in a 12-month period.[2-4] MDD can impact all aspects of an adolescent's life including academic functioning, social relationships, and family interactions.[2,5] The heightened risk of self-harm and suicide make adolescent MDD an important disorder to diagnose and treat.[5-7] Treatment to date, consisting of psychoeducation, psychotherapy, and pharmacotherapy have yielded suboptimal results in reducing the burden of disease, with clinical trials reporting high placebo response rates and rising adolescent suicide rates reflecting the need for ongoing evaluative research to identify the most effective treatments for the disorder.[5-11]

By definition, MDD is a complex disorder due to its numerous presenting symptoms and its impact on so many aspects of an adolescent's life. This consequently results in a myriad of outcomes that could be selected for measurement when designing a clinical trial. Depression symptom severity, to date, has been a common outcome measured in clinical adolescent MDD trials; yet, how different trials operationalize, measure, analyze, and report this outcome can vary significantly.[12-15] Furthermore, with no MDD biomarker available, MDD symptoms are typically determined through structured interviews and/or multi-informant questionnaires, which may be clinician-reported, parent- or teacher-reported or self-reported.[12,16] There is little overlap however, on symptoms across the wide variety of commonly used questionnaires that measure depression symptom severity or other possible depression outcomes.[14,17] This variable overlap may lead to research results that are unique to the particular questionnaire used, or to the construct measured by the questionnaire, rather than the symptom or disorder construct, thereby complicating the issue between outcome selection and how it is measured.[14,17]

The heterogeneity of outcomes selected and measured in adolescent MDD trials to date was quantified in a recent scoping review of all adolescent (ages 12 to 18 years) MDD randomized clinical trials (RCTs) published in the English language between 2008 and 2017.[18] In 42 articles describing 32 RCTS, 86 unique outcomes were measured.[18] These outcomes were categorized into an outcome classification taxonomy consisting of four core areas: (1) Physiological/Clinical; (2) Life Impact; (3) Resource Use; and (4) Adverse Events.[19] A fifth newly defined core area of "Individualized" (i.e., individual/personalized treatment goals) was added *post hoc* reflecting the growing move towards measurement of personalized outcomes. There was wide disparity in how these 86 outcomes were measured, with 118 different outcome measurement instruments (OMIs) used across the 32 RCTs.[18]

Different stakeholders and knowledge users, such as youth (inclusive of adolescents and young adults with lived experience with depression), caregivers (inclusive of parents and other primary caregivers), clinicians, funders, regulators, and policy makers can bring different priorities to outcome selection. Youth versus caregiver priorities may differ, while age, developmental level, and cultural background of patients may also lead to different priorities in the context of outcome selection.[12,15,20,21] To date, the clinician's perspective has been the key driver in measuring treatment change in adolescent MDD trials; however, this is changing with greater awareness of the value add of multi-informants on symptom change and the need to ensure that the measured treatment change is meaningful to the patients themselves.[12,15,16] There is also now greater awareness that a statistically significant difference on a specific scale between treatment groups does not necessarily translate into meaningful differences for patients and their families.[13,22,23] As such, patients (including children and youth) and caregivers are increasingly engaged in identifying important outcomes to select and measure, as well as defining what is meaningful change to them.[12,15,16,24,25] For example, patients and caregivers have been involved as full working group members alongside clinical and research experts at all stages of a consensus building process that was led by the International Consortium for Health Outcomes Measurement (ICHOM) to develop a standard set of outcomes for use in the clinical treatment of children and adolescents with anxiety and depression.[26] This move to incorporate greater patient engagement in defining outcome selection and measurement has led to a stronger emphasis on quality of life and functional outcomes as being critical to evaluate.[12,13,27]

The current variability in outcome selection, as well as in how and when outcomes are measured in adolescent MDD RCTs, can restrict the synthesis and interpretation of results through systematic reviews and meta-analyses, thereby limiting the ability to yield meaningful estimates of treatment effect and identify the most effective treatments.[15,28,29] A Core Outcome Set (COS), as defined by the Core Outcome Measures in Effectiveness Trials Initiative (COMET), is an agreed upon, standardized *minimum* set of outcomes that should be measured and reported in all clinical trials in specific areas of health or health care, while not precluding the inclusion of other outcomes.[30,31] COS development in other areas of medicine (e.g., rheumatology) has allowed for (a) increased consistency across trials; (b) maximized potential for a trial to contribute to systematic reviews of key outcomes; (c) increased measurement of outcomes important to stakeholders; and (d) reduced selective outcome reporting (which leads to biased estimates of treatment effects).[31,32] There is growing awareness of the need for COS in mental health;[29] for example, there is a COS for adult depression currently under development,[33] and a COS has been developed for adolescent bipolar disorder.[34] In addition, ICHOM has developed standard sets of outcomes for use in the routine clinical treatment of anxiety and depression in children and adolescents[26] and adults[35] with a large emphasis on feasibility of outcome measurement (e.g., short, free of charge OMIs). However, there is no COS as yet for use in adolescent MDD clinical trials. It is anticipated that development of an adolescent MDD COS for trials would similarly allow for enhanced comparison of trial results, maximize systematic reviews and meta-analyses, and thereby enhance the development of evidence-based clinical practice guidelines and policy changes ultimately leading to reduced disease burden.

OBJECTIVES

This study aims to employ COS methodology recommended by the COMET Initiative[30,31] and COnsensus-based Standards for the Selection of health Measurement INstruments (COSMIN),[36] with innovative adaptations to ensure engagement of youth and caregivers, to develop and implement a harmonized, evidence- and consensus-based COS for use in adolescent MDD clinical trials assessing any treatment intervention. This includes achieving consensus on "what" should be measured and reported in all MDD trials, followed by "how" and "when" these outcomes should be measured (Figure 1). A secondary objective is to develop guidance for incorporating youth and family engagement in the development of COS for adolescent mental health.

METHODS

Design

This project is called the International Network for Research Outcomes in Adolescent Depression Studies (IN-ROADS) and is registered with the COMET Initiative.[37] Important protocol amendments, if made, will be documented on Open Science Framework.[38] The COS development process will be led by the *COS Executive Group* and *Research Advisory Team* (Figure 2), which are composed of mental health clinicians and researchers (from a breadth of disciplines inclusive of psychiatry, psychology, pediatrics and nursing), methodologists/clinical trialists with experience in COS development in other pediatric areas, patient engagement advisors and research staff. Members from both groups are involved in designing and overseeing the development process of the COS, while the *COS Executive Group* provides executive oversight of all aspects of the project.

For the first stage of COS development, namely gaining agreement on what should be measured, we will follow the Core Outcome Set-STAndards for Development (COS-STAD) recommendations, described here using the Core Outcome Set-STAndardised Protocol Items (COS-STAP) reporting guideline (see Table S1).[39,40] In brief, this process involves (i) identifying candidate outcomes through a systematic review of outcomes in published clinical trials and consultations with youth and caregivers, (ii) eliciting views about the importance of the candidate outcomes, and (iii) obtaining consensus of the composition of the final small core set (Figure 1).

Process

Step 1. Outcome identification

We will first generate a list of candidate outcomes for evaluation in an international Delphi survey compiled from two sources: (a) the published literature[18] and (b) from youth and caregivers (Figure 1). A Delphi survey is an iterative multistage process that allows for consensus to be reached from a selection of disparate opinions, which is commonly used during the COS development process to prioritize important outcomes.[41,42]

Step 1a: From the published literature, we have identified 86 unique outcomes measured in clinical trials of MDD, as previously described (see Table S2). Many of these outcomes, however, are very

specific (e.g., relevant to a particular intervention type) and were often reported in only one trial. Delphi response rates have been shown to decrease when higher number of items (i.e., outcomes) are included for evaluation.[43] Therefore, we will convene a small group of stakeholders, the *International Advisory Group (IAG;* Figure 1) to prune (e.g., reduce) the number of these outcomes to a smaller list of generalizable outcomes for inclusion in the Delphi survey through a nominal group technique.[44] Members of the *IAG* will be identified by the *COS Executive Team* and the *Research Advisory Team* through their professional contacts, networks, and affiliations and will include representatives from key stakeholder groups inclusive of clinicians (e.g., psychiatrists, pediatricians, psychologists, social workers, nurse/nurse practitioners, etc.), clinical trialists, COS developers, systematic reviewers, journal editors, funders, and regulators. Recruitment will be monitored on an ongoing basis by the *COS Executive Group* to ensure that the final *IAG* includes broad representation across stakeholder groups and has geographic diversity.

The *IAG* will be asked to vote on which of the outcomes identified from the scoping literature review should be carried forward to the Delphi survey (i.e., which are sufficiently important and relevant to measure in any intervention type) through an electronic and confidential online survey. Prior to completing the survey, members will attend an initial virtual meeting to ensure clarity of the goals of the COS and how to complete the survey. Descriptions of each outcome developed by the *COS Executive Group* and vetted with members of the *Research Advisory Team* will be provided to the *IAG* to assist them in completing this step. Outcomes that meet an *a priori* threshold of $\geq$70% for inclusion will be included in the Delphi survey as "*scoping review generated"* outcomes. All other outcomes will not move forward to the Delphi survey (Figure 1). A follow-up virtual meeting (with embedded real-time polling available for remote participation) will take place if needed (e.g., the number of outcomes is not sufficiently reduced via the nominal group technique).

Step 1b: In a parallel process, outcomes for the Delphi survey will additionally and independently be identified through focus groups with youth and caregivers. Identifying candidate outcomes exclusively based on a systematic review of the literature risks prioritizing outcomes that are mainly relevant to trialists and researchers. Involving youth and caregivers early in the process is important to ensure that other important outcomes are not overlooked.[45] We will invite youth at different stages of their care pathway for MDD (e.g., early, mid-way, and post-treatment) and caregivers of youth who are currently attending, or who have previously attended ambulatory clinics at the research team's primary institutions and affiliated community clinics, to participate in these focus groups with a goal of understanding what outcomes they value most within the context of clinical research.

We aim to hold five to seven focus groups with approximately five to seven youth in each group and separately, five to seven focus groups with five to seven caregivers in each group. Each youth focus group will be stratified by age, gender, and stage of treatment, as possible. Ethics approval will be obtained and participants will be compensated for their time as per Strategy for Patient Oriented Research (SPOR) guidelines.[46]

Prior to attending the focus groups, general information (e.g., a one-page educational sheet, website, and a video) prepared in lay language will be shared with youth and caregivers to provide them with the details of what their participation in the project will entail and the value of their input on the development of a COS for adolescent MDD. At the beginning of each focus group, members of the research team and patient engagement advisors with group facilitation experience will review these materials and the goals of the session. With the support of group facilitators outcomes will be identified using a two-phase process:

1. Outcome theme generation: After a brief introduction on the concept of measurable outcomes in clinical research, group participants will be engaged in a general discussion about what outcome areas might be important to measure in adolescent MDD treatment trials. Participants will be asked to provide ideas and form themes about what are important outcome areas to measure. If specific outcomes are generated from the group, they will be mapped to the themes that emerge, with discussion with participants to ensure the outcome is being placed under the appropriate theme. Group facilitators will probe for other outcome themes. Participants will then be asked to write out a few "most important outcomes" for measurement, thereby ensuring input from even quiet or reluctant workshop participants.[47]
2. Outcome identification: Focus group participants will then be asked to share their written outcomes and suggest which theme to place it under; new themes will be developed as necessary. Facilitated discussion will follow to ensure the outcomes identified have been arranged according to the group participants' views, and where duplication occurs, discussion about the best wording that resonates with the participants will ensue.[47] Facilitators will facilitate the discussion to come to consensus of outcomes and outcome placement. Participants will have a final opportunity to comment on whether all important outcomes have been identified, and if important outcomes are missing further opportunity to add to them will take place.[48] All outcome themes and outcomes generated from each focus group will be carried forward to an outcome synthesis meeting (Step 1c; Figure 1).

Themes, outcomes, and all other ideas discussed in each focus group will not be shared between groups.

Step 1c: All outcome themes and outcomes generated through the course of the 10 to 14 focus groups will be carried forward to an outcome synthesis meeting with the *Youth & Caregiver Expert Advisory Committee (YCEAC;* Figure 2). The *YCEAC* will be comprised of three to four youths and three to four caregivers recruited from the focus groups. Patient engagement advisors previously involved as focus group facilitators will be identified as *YCEAC* co-chairs. All *YCEAC* members will be provided monetary compensation for their time, as per SPOR guidelines.[46] The *COS Executive Group* will work closely to support the *YCEAC* to synthesize all of the outcomes from the focus groups, deduplicate outcomes, and come to consensus of the final wording of the outcomes, ensuring that these are reflective of the "voices" of the focus group participants. These outcomes will be included in the Delphi survey as *"youth & caregiver generated"* outcomes.

Step 2. Preparation of outcomes for the international Delphi study

The *"scoping review generated"* and *"youth & caregiver generated"* outcomes will then be merged in preparation for the Delphi. As there will likely be overlap between some of the outcomes in the two lists, the *YCEAC* and the *COS Executive Group* will work together to determine where there is crossover, agree on the final wording of the outcomes, and develop definitions for any new outcomes identified from the focus groups.

Step 3. Outcome prioritization through the international Delphi Study

A multiple-round international electronic Delphi survey will be held in order to prioritize the list of candidate outcomes for the COS. A diverse and international group of professional stakeholders identified through the professional contacts, networks, and affiliations of the research team and the *IAG* will be invited to participate in the web-based Delphi study utilizing both chain-referral and purposive criterion sampling.[49] Invited participants will be able to circulate the invitation to their professional contacts (e.g., colleagues, networks, or organizations). Since specific guidelines for the number of participants to include in a Delphi study have not been established,[31,50] our aim is to recruit a representative sample of at least three individuals per professional stakeholder group (e.g., physicians [such as psychiatrists and pediatricians], psychologists, social workers, nurses/nurse practitioners, therapists, clinical trialists [inclusive of principal investigators/authors of past and any new clinical adolescent MDD trials], COS developers, biostatisticians, epidemiologists, systematic review/meta-analysis authors, journal editors, research ethics board members, funders, and regulators). Members of the *YCEAC* and other focus group participants will be invited to participate in the Delphi study in order to ensure youth and caregiver input. The list of Delphi study registrants will be consistently reviewed, and recruitment methods will be modified to ensure the appropriate distribution of stakeholders prior to Delphi study commencement.[51]

Approximately one month prior to the Delphi study, potential Delphi participants will complete a short electronic registration survey which will include an e-consent for study participation and document their experience in: (1) clinical trials design or conduct in mental health and other fields; (2) experience in caring for adolescents with MDD; (3) lived experience with depression;[51] (4) trial protocol/report authorship; (5) systematic reviews or evidence synthesis of clinical trials; (6) statistical analyses of clinical trials; (7) COS development; and (8) use of clinical trial publications for development of evidence-based clinical practices. Participants with experience in at least one of these areas will be eligible for Delphi participation. Only participants who fully complete a survey round will be able to proceed to subsequent rounds.

Each Delphi participant will be assigned a unique ID, known only to the survey administrator, to track participant retention across survey rounds. Participant anonymity will be maintained through the course of the study and all analyses of responses.[51] Participants who complete the Delphi surveys will be recognized by name, with their consent, in study publications.[51] Survey content and instructions will be in English. Each round will be conducted electronically via Research Electronic

Data Capture (REDCap) data management software,[52] with reminders over a three-week open-period to complete the survey.[53]

The merged list of *"youth & caregiver generated"* outcomes and the *"scoping review generated"* outcomes will form the candidate list of COS outcomes in the Delphi survey. For context, each outcome will be identified by its source (e.g., scoping review, youth/caregivers, or both) during all rounds of the Delphi survey. Delphi participants will be asked to rate the importance and feasibility separately of each outcome within the context of clinical effectiveness trials on a 9-point Likert scale with ratings of 1 to 3 identifying outcome is of limited importance or feasibility to measure, 4 to 6 representing moderate importance or feasibility, and 7 to 9 representing high importance or feasibility.[31] Outcome descriptions will be provided to the Delphi study participants to assist them in completing their ratings. Free-text boxes will allow participants the opportunity to provide feedback about the candidate outcomes.

Participants will have the opportunity to suggest additional outcomes only during the first Delphi round. Each outcome will undergo a minimum of two Delphi rounds, therefore, new items suggested in round 1 will require a third Delphi round to ensure that participants rate all outcomes twice. As current literature suggests that greater than three rounds results in lower participant response rates,[30] if no new outcomes are suggested in round 1, the Delphi will terminate after round 2 and outcomes not reaching consensus will be carried forward to the consensus meeting for voting. Each round will include free text boxes for participants to input additional feedback or explanation regarding their rating. Aggregate overall group results, individual scores for each outcome (e.g., median and percentage scoring of rating options), and anonymized feedback from free-text commentary from each round will be provided to participants for review in subsequent rounds. Providing feedback on initial Delphi results (without reference to any individual contributions) facilitates consensus, as participants will be able to re-consider and adjust their individual judgements in light of trends emerging within the wider group.[31]

Using COMET guidelines,[31] *a priori* decisions for data from each Delphi round on *consensus criteria* have been established: *Consensus in* occurs when $\geq$70% of participants score an outcome at 7-9 and <15% score an outcome at 1-3; while *consensus out* occurs when $\geq$ 70% participants score an outcome at 1-3 and <15% score an outcome at 7-9. All other results are considered to receive *no consensus.* Final analyses of the survey responses will include both aggregate overall group results and results stratified by stakeholder group via coding of responses for each self-reported stakeholder representation (e.g., clinician, funder, etc.).

Step 4. Consensus Meeting to Finalize COS

An in-person or virtual consensus meeting will be planned after completion of the Delphi study to finalize the recommended COS (Figure 1) and address the "*no consensus*" outcomes in order to finalize the COS. This meeting will bring together youth, caregivers, and professional stakeholder input to ensure the representation throughout COS development is incorporated in the final decision-

making on the content of the COS. Members of the *IAG* and *YCEAC* as well as Delphi study participants will be invited to the final consensus meeting thereby ensuring a wide range of international key stakeholders.

At the consensus meeting, the results from the Delphi study will be presented. Outcomes deemed *"consensus in"* through the Delphi study will only be discussed if one or more participant(s) feel strongly against the inclusion of the outcome and the meeting moderator feels that a vote is warranted based on the arguments presented. All outcomes that reached "*no consensus*" in the Delphi study will be discussed and undergo voting using real-time polling software. Moderated round table discussions of each outcome will take place followed by anonymous voting on each outcome as to: *"Include in COS"* or *"Exclude from COS".* After consensus meeting voting, outcomes reaching consensus for inclusion will be defined as ≥ 70% of participants voting *"Include in COS"* while exclusion of outcomes will be defined as ≥ 70% of participants voting *"Exclude from COS"*.[31] A second round of moderated round table discussion and anonymous voting will take place for outcomes not reaching consensus after the first round of voting. If outcomes do not reach consensus by the conclusion of the meeting, the final decision for inclusion or exclusion will be made by the *COS Executive Group*.

Based on published COS in other areas of pediatrics, we anticipate that the final COS may include approximately six to nine outcomes.[54] If the number of outcomes deemed critical is viewed as too large to feasibly incorporate into a COS (e.g., more than ~10 outcomes), we will use the results of the Delphi study to inform a discussion at the final consensus meeting in order to reduce the size of the COS. This may involve implementing stricter criteria for interpreting the Delphi findings (for example, ranking outcomes based on the mean numerical ratings).

Step 5. Establishment of Outcome Measurement Instruments (OMIs) for the COS:

The second stage of COS development is determining how to define and measure each outcome in the COS. We will follow the recommendations from COMET and COSMIN,[31,55] namely: (1) systematically identifying existing candidate measurement instruments for each outcome in the COS; (2) performing a quality assessment of the OMIs by evaluating the measurement properties and feasibility aspects of the OMIs; and (3) using consensus methods to select one OMI outcome for each COS. This process will be detailed elsewhere (e.g., Open Science Framework). In brief, to identify candidate OMIs, we will consult the following sources (i) the list of OMIs used in previous trials identified from the scoping review,[18] (ii) a rapid review for any new OMIs developed since then, and (iii) relevant measurement databases (e.g., PROMIS (pediatric item bank).[56] Candidate OMIs will be reviewed within the study team against the following criteria: face validity (e.g., is it meaningful as an indicator of the core outcome?); measurement properties (e.g., does it have good measurement properties using the COSMIN criteria?);[36,55] relevance (e.g., is it broadly relevant across comparative effectiveness trials of different intervention types?); and feasibility/acceptability (e.g., costs, available languages, length, type of administration). Consensus on suitability of an OMI for each outcome in the COS will be achieved by seeking input from the *IAG* through a virtual

meeting (with embedded real-time polling available for remote participation). The timing and frequency of measurement, which will be driven by the content of the final COS and its associated OMIs, will also be evaluated as part of this process. Where feasible and appropriate, youth and caregiver input will also be incorporated into the process.

It is possible that specific outcomes identified in the developed final COS will: (1) not have an OMI with sufficient measurement properties to adequately measure the outcome; or (2) not have an existing OMI to measure the outcome. Revisions to the initial COS based on this therefore may be required. For example, if there are outcomes deemed critical but for which there are no valid, reliable, relevant, and feasible OMIs, these outcomes will be highlighted in the final COS report as requiring urgent development of measurement instruments.[54,57]

Step 6. Reporting and Dissemination of the COS

The final COS and corresponding OMIs will be reported and disseminated world-wide to ensure that all adolescent MDD clinical trialists are aware of the newly developed COS.[30] Additionally, we recognize that there is an opportunity to develop guidance for incorporating youth and family engagement in the development of COS for adolescent mental health. International stakeholders attending the in-person consensus meetings will be actively engaged in the dissemination and uptake of the COS. A Knowledge Translation strategy that targets each stakeholder group with the goal of identifying champions, type of change required, as well as the necessary specific endorsement and enforcement strategies will be developed. Dissemination of the COS development work and recommendations in appropriate journals and at international/national conferences will be essential to promote uptake of the new COS in future adolescent MDD trials.

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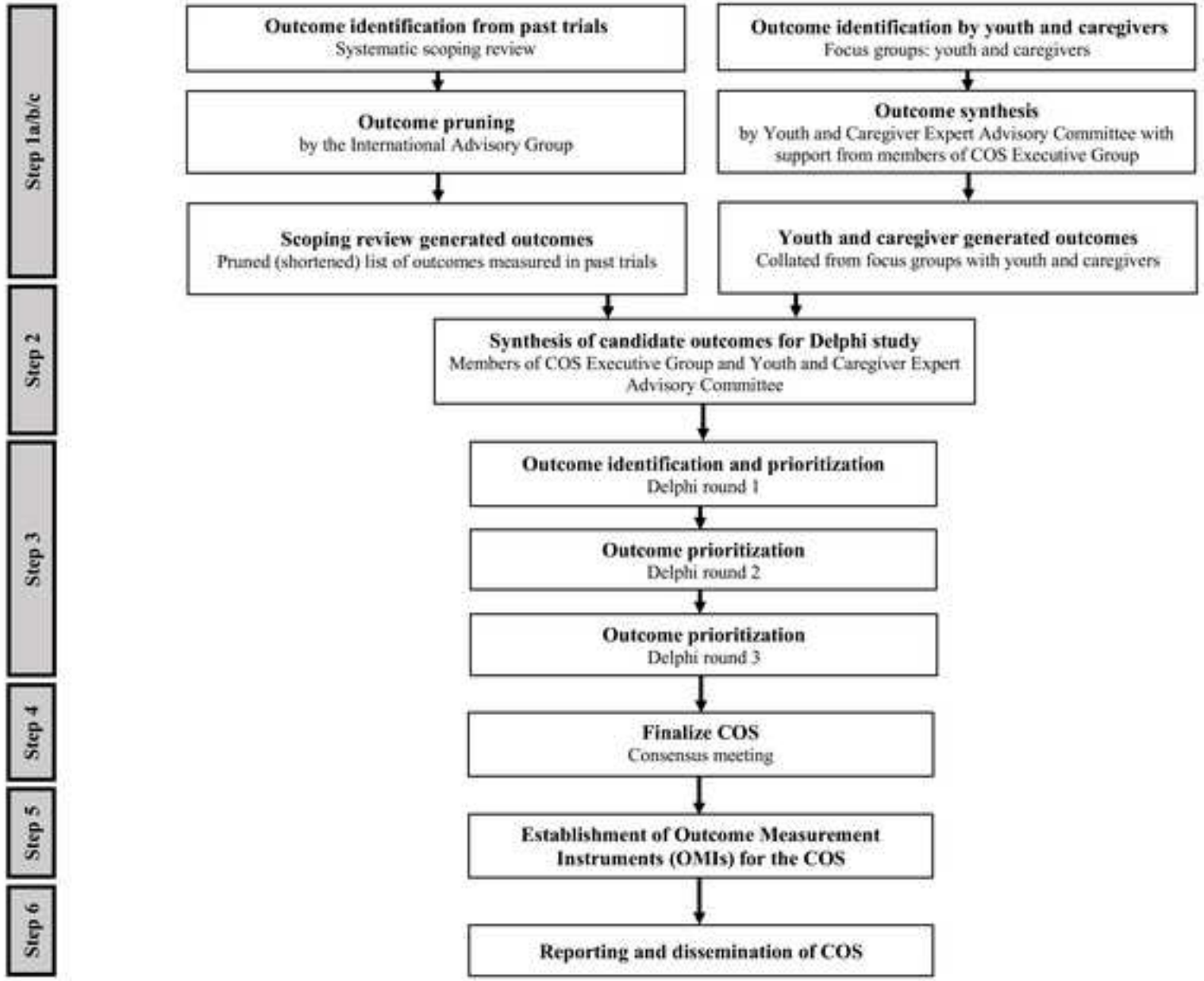
Figure 1. Outline of core outcome set development process.
Abbreviations: COS, core outcome set.

Figure 2. Core outcome set development team organizational chart.
Abbreviations: COS, core outcome set

Figure


Step 1a/b/c
Step 2
Step 3
Step 4
Step 5
Step 6
Outcome identification from past trials
Systematic scoping review
Outcome identification by youth and caregivers
Focus groups: youth and caregivers
Outcome pruning
by the International Advisory Group
Outcome synthesis
by Youth and Caregiver Expert Advisory Committee with support from members of COS Executive Group
Scoping review generated outcomes
Pruned (shortened) list of outcomes measured in past trials
Youth and caregiver generated outcomes
Collated from focus groups with youth and caregivers
Synthesis of candidate outcomes for Delphi study
Members of COS Executive Group and Youth and Caregiver Expert Advisory Committee
Outcome identification and prioritization
Delphi round 1
Outcome prioritization
Delphi round 2
Outcome prioritization
Delphi round 3
Finalize COS
Consensus meeting
Establishment of Outcome Measurement Instruments (OMIs) for the COS
Reporting and dissemination of COS

Figure

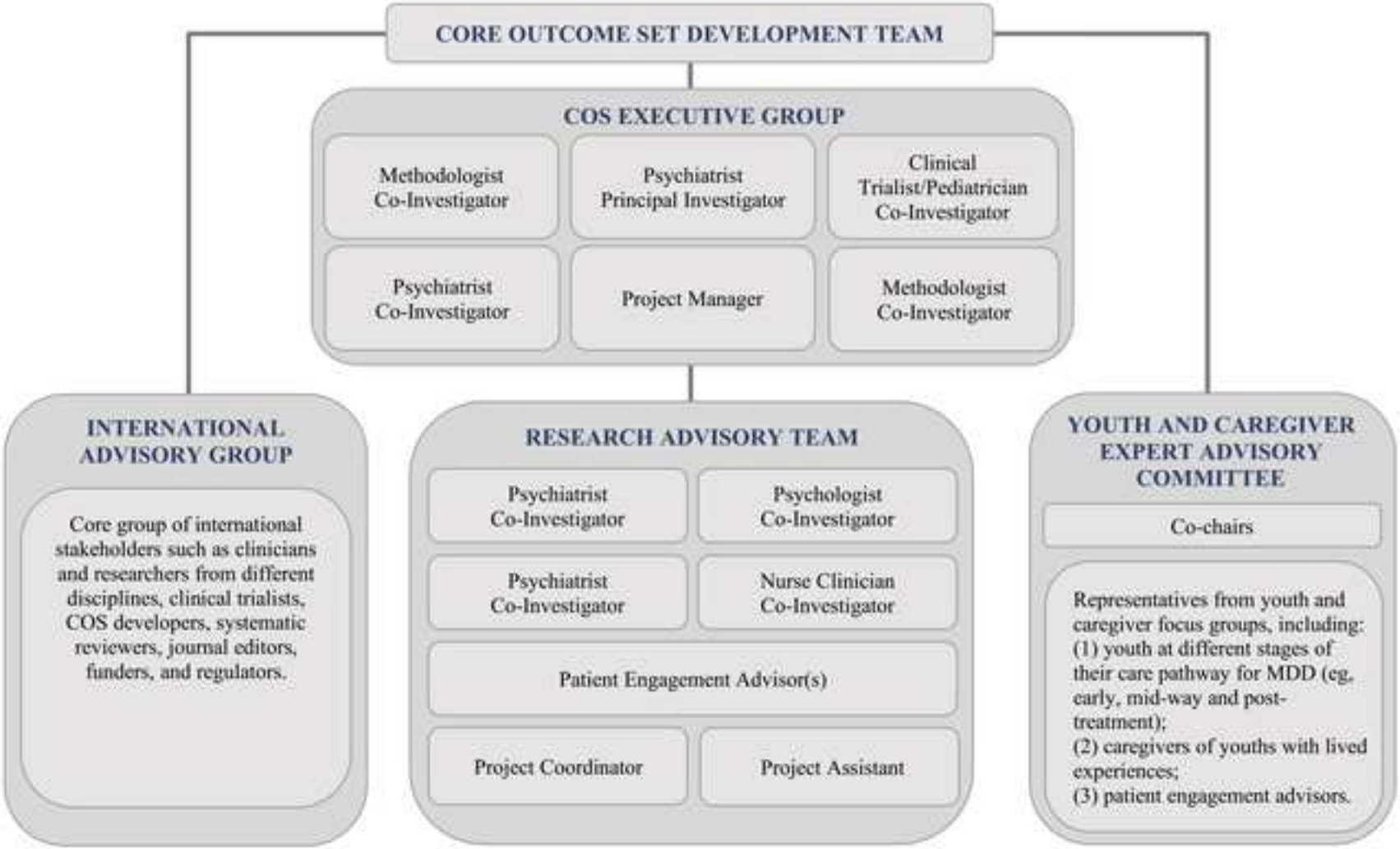

CORE OUTCOME SET DEVELOPMENT TEAM
COS EXECUTIVE GROUP
Methodologist Co-Investigator
Psychiatrist Principal Investigator
Clinical Trialist/Pediatrician Co-Investigator
Psychiatrist Co-Investigator
Project Manager
Methodologist Co-Investigator
INTERNATIONAL ADVISORY GROUP
Core group of international stakeholders such as clinicians and researchers from different disciplines, clinical trialists, COS developers, systematic reviewers, journal editors, funders, and regulators.
RESEARCH ADVISORY TEAM
Psychiatrist Co-Investigator
Psychologist Co-Investigator
Psychiatrist Co-Investigator
Nurse Clinician Co-Investigator
Patient Engagement Advisor(s)
Project Coordinator
Project Assistant
YOUTH AND CAREGIVER EXPERT ADVISORY COMMITTEE
Co-chairs
Representatives from youth and caregiver focus groups, including:
(1) youth at different stages of their care pathway for MDD (eg, early, mid-way and post-treatment);
(2) caregivers of youths with lived experiences;
(3) patient engagement advisors.

Table S1. Core Outcome Set-STAndardised Protocol Items (COS-STAP) checklist.[1]

Section	Item	COS-STAP checklist item	Location in manuscript
TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper describes the protocol for the planned development of a COS	Title
Abstract	1b	Provide a structured abstract	See Synopsis
INTRODUCTION			
Background and objectives	2a	Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation	Introduction
	2b	Describe the specific objectives with reference to developing a COS	Objectives, paragraph 1
Scope	3a	Describe the health condition(s) and population(s) that will be covered by the COS	Introduction, paragraph 1 and 2
	3b	Describe the intervention(s) that will be covered by the COS	Objectives
	3c	Describe the context of use for which the COS is to be applied	Objectives, paragraph 1
METHODS			
Stakeholders	4	Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study	Methods, *Process* subsection
Information Sources	5a	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference other protocols/papers	Methods, *Process* subsection
	5b	Describe how outcomes may be dropped/combined, with reasons	Methods, *Process* subsection
Consensus process	6	Describe the plans for how the consensus process will be undertaken	Methods, *Process* subsection
Consensus definition	7a	Describe the consensus definition	Methods, *Process* subsection
	7b	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process	Methods, *Process* subsection
ANALYSIS			
Outcome scoring/ feedback	8	Describe how outcomes will be scored and summarized, describe how participants will receive feedback during the consensus process	Methods, *Process* subsection
Missing data	9	Describe how missing data will be handled during the consensus process	Methods, *Process* subsection

Section	Item	COS-STAP checklist item	Location in manuscript
ETHICS and DISSEMINATION			
Ethics approval/ Informed consent	10	Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant)	Methods, *Process* subsection
Dissemination	11	Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination	Methods, *Process* subsection
ADMINISTRATIVE INFORMATION			
Funders	12	Describe sources of funding, role of funders	See Title Page
Conflicts of interest	13	Describe any potential conflicts of interest within the study team and how they will be managed	See *Manuscript Submission Form*

References for Table S1

1. Kirkham JJ, Gorst S, Altman DG, et al. Core Outcome Set-STAndardised Protocol Items: the COS-STAP Statement. *Trials.* 2019;20(1):116.

Table S2. Candidate outcomes for inclusion in core outcome set (COS) for adolescent major depressive disorder (MDD) randomized clinical trials (RCTs).

Core area	Outcomes (n=86)
Physiological/Clinical	Depressive symptom severity
	Depression treatment response
	Depression remission
	Depression relapse
	Time to relapse
	Time to remission
	Sleep disturbance
	Anhedonia
	Distress
	Dysfunctional thoughts
	Internalizing problems
	Rumination
	Self-esteem
	Anger
	Fatigue
	Hopelessness
	Irritability
	Negative mood
	Tension
	Anxiety symptoms
	Behavioural problems
	Presence or absence of substance use
	Obsessive symptoms
	Manic symptoms
	Global psychiatric treatment response
	Oppositionality
	Substance use severity
	Psychiatric diagnoses
	Global measure of current mental health status
	Suicidal ideation
	Global measure of self-injurious thoughts and behaviours
	Non-suicidal self-injury
	Respiration rate and capacity
	Heart rate
	Blood pressure
	Heart rhythm
	Vital signs
	Brain beta-nucleoside triphosphate levels
	Brain phosphodiester levels
	Brain phosphomonoester levels
	Serum norepinephrine levels

Core area	Outcomes (n=86)
	Serum serotonin levels
	Frontal lobe phosphocreatine levels
	Body fat
	Metabolic measures
	Lactate levels
	Urinalysis results
	Lab panel results
	Weight
	Height
	Physical examination
	Temperature
	Transdermal patch application site irritations
Life Impact	Overall functioning
	Family functioning
	Social functioning (overall)
	Social functioning with peers
	Electronic overuse
	Enjoyment of physical activity
	Assertiveness
	Vigour
	School functioning
	Ineffectiveness
	Problem solving
	Attention
	Energy expenditure
	Peak jump force and power
	Physical functioning
	Quality of life
	Treatment group attrition
	Participant treatment adherence
	Intervention satisfaction
	Treatment quality/fidelity
	Therapeutic alliance
	Attitudes on treatment plan change
	Child and parent treatment expectations and amount treatment helped
Resource Use	Service use by participant
	Medications used
	Quality of care received
	Cost-effectiveness of study interventions
	Total cost of resources used by participant
	Costs of study interventions
	Service use by primary carer
	Total costs of resources used by carer

Core area	Outcomes (n=86)
Adverse Events	Adverse events
Individualized[a]	Individual/personalized outcomes

[a] Proposed new core area; not part of the Dodd and colleagues (2018)[1] framework

References for Table S1

1. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. *J Clin Epidemiol.* 2018;96:84-92.