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Measuring What Matters: Development and Dissemination of a Core Outcome Set for Pediatric Anxiety Disorder Trials

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RH = Measuring What Matters

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DEI

Supplemental Material

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Diversity & Inclusion Statement: We worked to ensure sex and gender balance in the recruitment of human participants. We worked to ensure race, ethnic, and/or other types of diversity in the recruitment of human participants. We worked to ensure that the study questionnaires were prepared in an inclusive way. One or more of the authors of this paper self-identifies as a

member of one or more historically underrepresented racial and/or ethnic groups in science. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented sexual and/or gender groups in science. We actively worked to promote sex and gender balance in our author group. We actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our author group. The author list of this paper includes contributors from the location and/or community where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.

The research was performed with permission from The Hospital for Sick Children Research Ethics Board.

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INTRODUCTION:

Prevalence rates for pediatric anxiety disorders vary from 9.4% to 20.5% worldwide.¹⁻³ With a median age of onset of 11 years,^{4,5} pediatric anxiety disorders significantly impact all aspects of a child's life, including their social, academic and family functioning.^{6,7} They are chronic disorders, with significant co-morbidity, often persisting into adulthood, resulting in impairments in adult social, educational, and occupational functioning.⁵⁻⁹ Although evidence supports the most commonly used psychological treatments, (e.g., cognitive behaviour therapy [CBT]), or pharmacological treatments (e.g., selective serotonin reuptake inhibitors), there are notable concerns with the research to date, which include the relatively small body of evidence, the brief follow-up time of most trials, as well as the use of many different symptom rating scales across studies to assess improvement.^{6,10}

A major concern across trials in all areas of medicine is the wide variability that exists in outcome selection, measurement, analysis, and reporting.¹¹⁻¹⁴ Amongst mental health trials, there is little overlap in selected outcome measurement instruments (OMIs) measuring major concepts such as symptom severity or functioning.^{15,16} Research results from one trial therefore, may be unique to the particular OMI used, or to the specific construct measured by the questionnaire or scale,^{15,16} further impairing comparison of results between studies. Additionally, when it comes to measurement across pediatric anxiety disorders, capturing dimensionality across the various anxiety disorders, fluctuation of symptoms over time, as well as the longitudinal stability of symptoms are all critically important. Current heterogeneity in outcome selection and measurement across trials limits the comparison of treatment effects, evidence synthesis, and ultimately hinders the translation of research into clinical practice,^{11-14,17} highlighting the need for outcome standardization and the importance of identifying one OMI for any selected outcome.^{16,18,19}

Across both pediatric mental health clinical care and research, there is also growing awareness of the value of multi-informant perspectives on symptom change and the need to ensure a meaningful difference for patients beyond reporting statistically significant differences in treatment groups.^{12,14,20-22} As such, patients and families are increasingly engaged in defining what is meaningful change to them and selecting what are important outcomes to measure in their care as well as in trials.^{12,14,21,23}

Recognition of the need for and importance of outcome standardization in pediatric mental health disorders is evolving and there are several initiatives of importance to note. The International Consortium for Health Outcomes Measurement (ICHOM) has developed standard outcome sets for use in routine clinical treatment of various mental health conditions including anxiety, depression, obsessive compulsive disorder, and post-traumatic stress disorder in children and adolescents²⁴ and adults.²⁵ These standardized sets for routine clinical care focus on easy implementation in a variety of contexts (e.g., low-income countries); feasibility (e.g., single set of outcomes across four diagnoses); and acceptability (e.g., prioritizing OMIs that are short, widely translated, and free of charge).²⁶ Many widely used OMIs (e.g., Beck Anxiety Inventory), of note, were not chosen due to not meeting these criteria (e.g., costs).²⁷

Importantly, the context and requirements of clinical trials are quite distinct from those of routine care. For example, academic or industry funding is typically available to support assessor training and OMI licensing, if needed; there is typically dedicated, compensated time in trials for obtaining comprehensive, sensitive outcome assessments; and clinical trial OMIs must meet specific (e.g., regulatory) requirements to ensure that the validity, reliability, and responsiveness of measurements are maximized. Amongst clinical trials in other areas of medicine, development of a Core Outcome Set (COS) has been a solution to address heterogeneity in outcome selection and measurement. A 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 trials in specific areas of health or health care, while not precluding the inclusion of other outcomes.^{28,29} In other areas of medicine (e.g., rheumatology), the development of a COS 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 knowledge users, including patients and their families; and (d) reduced selective outcome reporting, which can lead to biased estimates of treatment effects.^{29,30} Pediatric mental health trials; however, critically lag behind.

Highlighting the growing interest among funders and regulators to establish common measures across trials, the International Alliance of Mental Health Funders³¹ have begun to advocate for the use of the Revised Child and Adolescent Anxiety and Depression Scale Short Form (RCADS-25)³² in youth anxiety and depression research they fund.^{33,34} Use of this one OMI across two complex and heterogeneous disorders without clarity as to what outcome it is meant to measure, its relevance and meaning to youth and families,³⁵ or its fitness as a trial OMI, however, does not fully address the need for a tailored and comprehensive COS for trials across the spectrum of pediatric anxiety disorders.^{12,19}

OBJECTIVES

The objective of the COMPACT (Core Outcomes and Measures in Pediatric Anxiety Clinical Trials) Initiative is to develop a harmonized, evidence- and consensus-based COS that is meaningful to youth and families for use in future trials in pediatric anxiety disorders. The study will identify “what” outcomes, at a minimum, should be measured and reported in all future trials in pediatric anxiety disorders following the framework of COMET²⁹ and OMERACT Filter 2.1 for COS development³⁶ and will identify “how” endorsed outcomes should be measured by identifying fit-for-purpose OMIs (e.g., valid, reliable, responsive, and feasible) using Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) standards^{37,38} and international recommendations for guiding the selection of OMIs for COS.³⁷⁻³⁹

METHODS

Study Design: An integrated mixed-methods design, including literature scoping review, and quantitative and qualitative consensus approaches, with a focus on meaningful engagement of youth and families as full research partners will be used. The COMPACT Initiative will follow international best-practice guidelines for developing^{40,41} and reporting⁴² COSs, adapted from COMET,^{28,29} OMERACT^{30,38,39} and COSMIN⁴³⁻⁴⁶ guidance for COS development. This project is registered with COMET.⁴⁷ Important protocol amendments, if made, will be documented on Open Science Framework.⁴⁸ See Supplementary Table 1 for the Core Outcome Set-Standardised Protocol Items (COS-STAP) checklist.⁴¹

Process:

Step 1 - Identification and Prioritization of Outcomes: Identification of what outcomes to measure will be carried out in three phases following recommendations from the Core Outcome Set-STAndards for Development framework^{29,40} as outlined below. See Figure 1 for an overview of planned steps.

Phase 1a Identification of Candidate Outcomes Through a Scoping Review: Following the COMET framework,^{28,29} we will conduct a scoping review of the literature to systematically identify candidate outcomes and OMIs through a comprehensive search of electronic bibliographic databases to identify published trials in pediatric anxiety disorders in the last 10 years. Citations retrieved will be screened against prespecified inclusion/exclusion criteria by two independent reviewers with the aim to extract reported candidate outcomes and OMIs used.

Phase 1b Identification of Youth and Family Outcomes: In parallel to the scoping review, virtual workshops will be conducted through a secure virtual platform to identify outcomes important to youth with anxiety disorders' lived experience and family members of youth with anxiety disorders' lived experience. Upon appropriate Research Ethics Board approval, international recruitment of youth aged 8 to 24 years with anxiety disorders' lived experience and family members of youth 4 to 18 years with anxiety disorders' lived experience for participation in workshops will be through 1) clinical sites and 2) patient engagement partners and their networks. We will use a variety of platforms including posters, social media, and project website to ensure diverse engagement of youth and families. We will also establish a national committee of youth and family members to serve as active research partners through the entire project course and who will advise on all aspects of youth and family engagement and recruitment (e.g., informed consent, educational materials, co-facilitate youth and family workshops, attend consensus meetings, etc.).

Workshop Design: Four workshops of 8 to 10 participants each will be held separately for: 1) younger youth (8 to 12 years); 2) older youth (13 to 17 years); 3) transition-aged youth (18 to 24 years); and 4) family members, for a total of 30 to 40 participants per each of the four participant groups (120 to 160 total). Purposive sampling will be employed to ensure wide representation across participant characteristics (e.g., age, sex and gender, race), as outcomes of importance may differ across characteristics. As the aim of these workshops are to invite youth and families to identify treatment outcomes that matter to them, and not meant to assert the prevalence of preferences of outcomes in populations, we anticipate that between 20 to 40 purposively sampled participants in each group (younger youth, older youth, transition-aged youth, and family members) will result in saturation of outcomes being identified.

Our Youth and Family Advisory Committee will co-design and co-facilitate developmentally appropriate workshops for use with each group, which will include fun and engaging ice-breaker activities. As part of these workshops, we will provide education on outcomes and outcome selection in clinical research and facilitate age-appropriate discussion about outcomes that participants feel are important to select and measure.

Workshop Data Synthesis: Workshops will be transcribed verbatim and analyzed using a reflexive thematic analysis approach.⁴⁹ To authentically capture the experiences of workshop participants, a thematic approach will be conducted inductively. Transcripts will be independently coded by three reviewers, with regular analysis meetings to reach consensus. Emerging themes will be verified by research team members with professional experience (e.g., clinicians and researchers) and members of our youth and family advisory committees with lived experience with the goal of generating youth and family outcomes.

Outcomes generated through the workshops will be carried forward to an outcome synthesis meeting with our Youth and Family Advisory Committee, who will review all workshop outcomes, de-duplicate outcomes, and finalize definitions and wording of outcomes.

Phase 2 Delphi Study - Identification and Prioritization of Outcomes: In order to identify and prioritize outcomes generated from Phase 1, as recommended for COS development,⁵⁰⁻⁵² we will conduct an international, web-based Delphi Study using an iterative systematic multistage process that facilitates consensus through engagement of knowledge users inclusive of youth and family members.^{36,50-53} Candidate outcomes generated from both the scoping review and workshops will be merged into one list for the Delphi and identified as coming from the scoping review, or youth and families.

Delphi Study Description: We will recruit a wide and international group of knowledge users and stakeholders, including clinicians, trialists, methodologists, and others, as a “Clinicians/Researchers Delphi Group”, all of whom will help to further disseminate invitations through their expansive professional contacts, networks, and affiliations. Participants will be purposefully sampled using combined snowball sampling and purposive criterion sampling⁵⁴ to ensure adequate geographical and demographic representation.⁵⁴ Recruitment of a “Youth and Family Delphi Group” will be facilitated through clinical sites and national youth/family engagement partners. Our Youth and Family Advisory Committee will co-design educational materials for use with youth and families in preparation for Delphi participation, and will pilot-test the Delphi to ensure language and structure are youth and family-friendly.²³ Participant confidentiality will be maintained for all analyses through the course of the study.

Although there is no consensus on the number of Delphi participants required,⁵⁵ the majority of COSs developed to date have achieved samples in the 100 to 200 participant range for their Delphi studies.⁵⁶ Delphi participants will be asked to rate the importance of each outcome within the context of clinical effectiveness trials on a 9-point Likert scale with ratings 1 to 3 identifying outcome is of limited importance to measure, 4 to 6 representing moderate importance, and 7 to 9 representing critical importance.²⁹ Free-text boxes will allow participants to provide comments on candidate outcomes in each round. In the first round only, participants will be asked to suggest new candidate outcomes. Anonymized feedback (e.g., quantitative counts and qualitative response from textboxes) from previous rounds will be fed back to participants in subsequent rounds, allowing participants to re-consider and adjust their individual judgements in light of trends emerging within the wider group.²⁹ If necessary, a third round will be held to evaluate any new candidate outcomes introduced in round 1 and only rated in round 2, thereby ensuring all items are evaluated twice.

Delphi Data Analysis: Using COMET,^{28,29} *a priori* decisions from each Delphi round on outcome prioritization criteria have been established: “Outcome In” occurs when $\geq 70\%$ of participants score an outcome at 7-9 and $<15\%$ score an outcome at 1-3; while “Outcome 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” on whether the outcome is sufficiently important to be part of a COS, or if it should be dropped from further consideration. As per COMET recommendations,^{28,29} final analyses of responses will include aggregate overall group results and weighted results stratified by the two primary knowledge user groups (“clinicians/researchers” and “youth/family”) to ensure equal representation via coding of responses for each self-reported knowledge user representation.

Phase 3 COS Outcome Finalization: Following best practices for COS development, an expert virtual meeting, will be held to review the Delphi findings and reach consensus on a final COS that is acceptable and feasible for use. To allow for round-table discussion we will invite a maximum of 30 participants that will include youth and families, in addition to clinicians/researchers, clinical trialists (academic and industry), and other stakeholders who can support or mandate COS use, (e.g., funders, regulators, and journal editors).

“No Consensus” outcomes (e.g., outcomes that do not reach consensus in the Delphi study) will be presented with the goal of conducting moderated round table discussion amongst meeting attendees followed by anonymous real-time voting as to “Include in COS” or “Exclude from COS. Outcomes deemed “Outcome In” or “Outcome out” will only be brought forward for discussion if attendees feel strongly that they warrant discussion at the meeting.

Meeting Data Analysis: After discussion and real-time anonymous voting during the meeting, outcomes reaching consensus for inclusion will be defined *a priori* as $\geq 70\%$ of participants voting “Include in COS” while exclusion of outcomes will be defined as $\geq 70\%$ of participants voting “Exclude from COS”.²⁹ A second round of moderated round table discussion and anonymous voting will take place for outcomes that remain “No Consensus” after the first round of voting. Published pediatric COSs have typically included between 6 to 9 outcomes,⁵⁷ a benchmark for how many outcomes should be carried forward from the meeting.

Step 2 - Identification of Outcome Measurement Instruments for the COS: Identification of how to measure final selected outcomes will be carried out in three sequential phases following internationally developed and recognized standards set by COSMIN^{37,44,45} as outlined below.

Phase 1 Screening of OMIs: To ensure that there are no new OMIs developed in the interim from the time of the scoping review, we will perform a rapid review for any new OMIs developed, including searching relevant measurement databases (e.g., PROMIS Pediatric Instrument Banks).⁵⁸ The large list of candidate OMIs will be reviewed against the selected core outcomes to evaluate for: (i) content validity and (ii) feasibility of use. Those that pass this screen will move forward for a more comprehensive, albeit brief psychometric evaluation in Phase 2.

Phase 2 Psychometric Appraisal of Short-listed OMIs: The focus of this phase is to systematically identify and provide an overall synthesis of the breadth and quality of evidence on the measurement properties of the short-listed candidate OMIs following internationally endorsed standard COSMIN methodology.^{19,37,38} With the aim of establishing one OMI with sufficient measurement properties for each outcome in the final COS, we will complete a focused assessment of commonly used OMIs to briefly review key measurement properties (e.g., validity, reliability, and responsiveness to change) and evaluate the quality of evidence for these key measurement properties.

Phase 3 Expert Meeting to Review and Endorse OMIs: An expert virtual meeting will be held to review the findings of the quality review of candidate OMIs and reach consensus on the final OMI recommendations. To allow for round-table discussion and anonymous voting, we will invite a maximum of 30 key knowledge users, including experts in measurement science, pediatric anxiety disorders (clinicians and researchers), clinical trialists, funders and regulators through purposeful sampling and invitation. Youth and Family Advisory Committee members will also be invited to attend. Round table discussion will take place with a goal to achieve consensus as to which OMI should be used for each outcome through anonymous real-time voting. To ensure widespread involvement in the final consensus decision on the OMIs, we will also have an open, international review period of the final recommendations from the expert group posted on Open Science Framework⁴⁸ with a call for written comments thereby allowing for scientific, and youth and family community input before the OMIs are finalized and disseminated.

It is possible that specific outcomes identified in the developed final COS will either not have an OMI with sufficient measurement properties to adequately measure the outcome, or there may not be an existing OMI to measure the outcome. 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.^{38,57}

Step 3 – COS Dissemination:

Knowledge translational and dissemination activities will be guided in collaboration with our Youth and Family Advisory Committees and other international knowledge users through all phases of the study.

Educational materials co-developed with our Youth and Family Advisory Committee for this project, will enable us to create an open-access COS Educational Manual consisting of capacity-building educational deliverables and “best-practice” resources for use by COS developers in future pediatric mental health COS development. These resources will further advance how youth and families are engaged in pediatric mental health COS development, given the importance placed on this by the COMET Initiative.²⁹

The freely and widely available COS, inclusive of outcomes and OMIs, will be hosted on the COMET database,²⁸ which collates and hosts all developed COSs, and which trialists and knowledge users search to find relevant COSs for their population of interest. We will raise awareness of the COS via dissemination through our advisory committee members, project partners and their networks, community stakeholders and the larger academic/scientific community via a variety of media platforms (e.g., journal papers and academic presentations, press releases, virtual webinars, social media platforms, infographics, video animations, policy briefs, web content and plain language summaries). Greater outcome standardization across future trials in pediatric anxiety disorders will ultimately enhance the development of evidence-based clinical practice guidelines.

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Figure 1. Timeline for completion of the study.

Journal Pre-proof

STUDY SYNOPSIS

Introduction Summary

Pediatric anxiety disorders (AD) are prevalent disorders impacting all aspects of a child's life and functioning.¹ Although evidence supports commonly used treatments, there are notable concerns with the research to date.² Heterogeneity in outcome selection, measurement, analysis, and reporting is a contributing factor to the hinderance of the translation of research into clinical practice.³

Recognition for outcome standardization in pediatric mental health disorders is evolving and there are several initiatives of importance, including The International Consortium for Health Outcomes Measurement (ICHOM), which has developed standardized outcome sets for use in the routine clinical mental health treatment of children and adolescents.⁴ Similarly, the International Alliance of Mental Health Funders⁵ advocate for use of one specific outcome measurement instrument (OMI) in youth mental health research they fund.

Development of a Core Outcome Set (COS), a minimal set of outcomes that should be measured and reported in clinical trials, has been a solution in other areas of medicine to address heterogeneity in outcome selection and measurement across trials.⁶ The COMPACT (Core Outcomes and Measures in Pediatric Anxiety Clinical Trials) Initiative will develop a harmonized, evidence- and consensus-based COS that is meaningful to youth and families for use in future trials in pediatric AD.

Method Summary

An integrated mixed-methods design, including literature scoping review, quantitative, and qualitative consensus approaches, with a focus on meaningful engagement of youth and families as full research

partners will be used. We will follow international best-practice guidelines for developing and reporting COSs, adapted from COMET,⁶ and COSMIN⁷ guidance for COS development. This project is registered with COMET.⁸

First, we will conduct a scoping review of the literature by completing a comprehensive search of electronic bibliographic databases to identify published trials in pediatric AD in the last 10 years, with the goal to systematically identify candidate outcomes and outcome measurement instruments (OMIs) used across trials to date. In parallel, virtual workshops will be conducted through a secure virtual platform to identify outcomes important to youth with anxiety disorders' lived experience aged 8 to 24 years and family members of youth aged 4 to 18 years with anxiety disorders' lived experience. We will establish a national committee of youth and family members to serve as active research partners through the entire project, who will advise on all aspects of youth and family engagement and recruitment. Workshops will be held separately for youth of different age groups and separately for family members. The aim of these workshops is to understand what treatment outcomes matter to youth and families. Our Youth and Family Advisory Committee will co-design and co-facilitate developmentally appropriate workshops for use with each group and review all workshop outcomes to finalize outcome definitions and wording.

We will then conduct an international, web-based Delphi study using an iterative systematic multistage process that facilitates consensus through engagement of knowledge users inclusive of youth and family members.⁹ Candidate outcomes generated from the scoping review and workshops will be merged into one list and identified as coming from the scoping review, or youth and families. Following COMET⁶ guidelines, *a priori* decisions from each Delphi round for "Outcome In" and "Outcome Out" will be established. An expert virtual meeting will be held to review Delphi findings and reach consensus on acceptable and feasible for use outcomes that will make up the final COS.

In a second step, we will identify how each outcome in the final COS is to be measured. We will perform a rapid review of relevant measurement databases to ensure no new OMIs were developed since the scoping review. The list of candidate OMIs will be reviewed against the selected core outcomes to evaluate for: (i) content validity and (ii) feasibility of use. We will identify and synthesize aspects of the quality of evidence on the measurement properties of the short-listed candidate OMIs to inform the ultimate selection of one valid, reliable, and responsive for use OMI for each outcome in the COS for future trials in pediatric AD. An expert virtual meeting will be held to review the findings of the brief quality review of candidate OMIs and reach consensus on final OMI recommendations.

Significance Summary

Knowledge translational and dissemination activities will be guided in collaboration with our Youth and Family Advisory Committee and other international knowledge users through all phases of the study. The freely and widely available COS will be hosted on the COMET database.¹⁰ Greater outcome standardization across trials in pediatric AD will ultimately enhance the development of evidence-based clinical practice guidelines.

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