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A waitlist randomised control trial of the unified protocol for the treatment of emotional disorders in children and adolescents with chronic medical conditions (The UP-CAM Study): protocol paper

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Abstract

Background Children and young people with chronic medical conditions (CMCs) are at a greater risk of experiencing emotional disorders (e.g., anxiety and depression) compared to their healthy peers. Transdiagnostic interventions show promise to effectively treat these symptoms, but evidence supporting their use in children and young people with CMC populations is limited. This study aims to adapt and pilot the feasibility, acceptability, and appropriateness of the Unified Protocol for the Treatment of Emotional Disorders in Children and Adolescents (UP-C/A), a transdiagnostic intervention, in children and young people with CMCs. Further, it aims to assess the efficacy of the UP/CA in a randomised control trial (RCT) and examine the influence of this treatment on functional outcomes.

Methods The UP-C/A will be adapted using feedback from people with lived/living experience of CMCs (e.g., parents and adolescents), clinicians, and medical professionals working with this population. Participants are children and young people (8 years– 17 years, 11 months old) with a CMC and co-occurring anxiety and/or depressive symptoms. An internal pilot design will be implemented, with the first six participants of the RCT serving as the pilot sample (3 for each group). The RCT participants will be randomised to either a treatment group ($n=30$) or waitlist control group ($n=30$) and will receive the UP-C/A immediately and eight weeks after enrolment, respectively. Participants will receive 8 to 21 sessions of the intervention, delivered weekly to fortnightly by a trained psychologist. Parent and

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child-reported measures will be collected at four timepoints: baseline, 8 weeks, immediately post-intervention, and at 3 months post-intervention.

Discussion No RCT has evaluated the efficacy of the UP-C/A in children and young people with CMCs. We anticipate that the UP-C/A will be effective at treating anxiety and depression symptoms in children with CMCs, and that short-term gains will be maintained at 3 months post-intervention and be associated with better functional outcomes (e.g., adaptive behaviour and self-regulation). If found to be efficacious, the UP-C/A could be adopted for broad use in public health settings and beyond to help treat emotional disorders in children and adolescents with CMCs.

Trial registration Australian and New Zealand Clinical Trials Registry: 12,624,000,114,549; Date: February 23, 2024. WHO Universal Trial Number: U1111-1285-0860.

Keywords Randomised Controlled Trial, Chronic Medical Conditions, Emotional Disorders, Anxiety, Depression, Transdiagnostic Intervention, Unified Protocol, Children, Young People, lived experience consultation

Introduction

Emotional disorders such as anxiety and depression are major health challenges in children and adolescents (or young people), with prevalence rates of 15–20% [1] and 2.6–14% [2], respectively [3]. Prevalence rates are almost three times higher in children and young people with chronic medical conditions (CMCs, 20–50%) such as epilepsy, asthma, sickle cell disease, stroke, brain injury, and cystic fibrosis [3–5]. In young people with CMCs, emotional disorders are associated with negative physical and medical outcomes due to poorer medication adherence, longer hospital stays, worse hospital outcomes, and increased risk of self-harm [3]. Additional consequences include reduced social participation, cognitive function, academic performance, physical function, sleep, quality of life, and long-term well-being [3, 6, 7]. Together, these implications highlight the need for targeted psychological interventions in young people with CMCs.

Mental health interventions in young people often employ a traditional cognitive behaviour therapy (CBT) approach and focus on a single diagnosis or diagnostic category such as anxiety (e.g., Cool Kids for anxiety disorders [8], Coping Cat [9], and the Child-Adolescent Anxiety Multimodal Study [10]). These diagnosis-specific protocols fail to address the complex mental health needs of children and young people who present with multiple, overlapping, or co-occurring emotional disorders [3, 11], often necessitating additional treatments for the latter [12]. While CBT diagnostic specific programs show initial success, they have high rates of relapse, potentially due to a focus on specific symptoms rather than the underlying emotional problem [13, 14]. Another limitation of these interventions is the shortage of clinicians trained to deliver them, since the financial and time costs of training for different problem areas are high [15, 16].

To address these challenges, there has been growing emphasis on transdiagnostic interventions [17], which enable the treatment of co-occurring conditions, help reduce the risk of relapse and are generally more cost- and time-efficient [18]. Transdiagnostic interventions often include an integration of effective evidence-based therapies designed to treat the underlying factors that are common to many emotional disorders [19]. They are based on the principle that various emotional disorders have shared underlying risk factors including biological, psychological, temperamental, cognitive, and environmental factors [20, 21], and are designed to be flexible and adaptable enough to simultaneously treat co-occurring mental health concerns such as anxiety and depression [21]. Sufficient evidence demonstrates their efficacy in adults [22] and typically developing young people [11, 16].

The Unified Protocol (UP) for the Treatment of Emotional Disorders in Children (UP-C) and Adolescents (UP-A) is a manualised CBT-based transdiagnostic protocol, adapted from the original Unified Protocol (UP) for adults [23, 24]. The UP-C/A targets core dysfunctions underlying many emotional disorders with the aims of increasing emotional awareness and cognitive flexibility and limiting the use of avoidant coping responses to negative emotional experiences [12, 25]. The efficacy of the UP is well-established in several randomised control trials (RCTs) involving adults [16, 23, 26], and emerging studies show promising outcomes in the UP modified for children and adolescents [11–13, 27–31]. Specifically, studies in children and adolescents (including 9 RCTS) mainly demonstrate the efficacy of the UP-C/A for anxiety and depression symptoms [11, 13, 18, 28–32], with others showing its efficacy for irritability [33], serious mental health illness [34], obsessive compulsive disorder [28], and post-traumatic stress disorder [35]. Since children with CMCs face a higher risk of multiple mental health concerns [3, 5, 36], having access to a single treatment that addresses various concerns can substantially enhance their outcomes and reduce the heavy financial and time burden on the family and child, allowing more time for school and other activities [37, 38]. To date however, only one case study ($n = 2$) has demonstrated its effectiveness in young people with chronic pain [39],

indicating the need for RCTs testing the efficacy of this intervention in children and young people with CMCs.

Adapting/modifying the UP-C/A to ensure its suitability for young people with CMCs before testing its efficacy is essential given the challenging reality of managing a CMC. This includes a range of complex demands, such as intricate medication schedules, continuous symptom monitoring, dietary restrictions, frequent medical and mental health appointments (often resulting in missed school), and significant time and financial burdens that impact the health-related quality of life (HRQoL) of both the young people and their families [38, 40]. These children and young people frequently experience negative emotions such as fear, shame, and sadness, stemming from a sense of being different from their peers, which can contribute to low self-esteem and depressed mood [41]. The impact of the illness, perceived burden of treatment, inability to accurately judge the severity of their symptoms, developmentally appropriate desire for independence, and other competing demands (e.g., school and social responsibilities) may also affect their adherence to medical treatment and impact their mood [7, 40]. Additionally, many children experience sleep problems, pain, and/fatigue from their condition or must undertake uncomfortable medical procedures to monitor or improve their health (e.g., blood test, etc.). Parental distress, along with the child's co-occurring physical and mental health symptoms, significantly affects the well-being of children with CMCs [3, 7, 40, 41], underscoring the need for holistic, family-focused psychological interventions and evaluations. Stakeholders, including families and young people with lived experiences of CMCs, clinicians and medical professionals working with this population must be involved in adapting evidence-based interventions to ensure that they effectively address their care priorities [31, 42]. Lengthy public health waitlists for young people accessing mental health care in Australia and globally [43–45], alongside limited specialist services for young people with CMCs, highlight the need to demonstrate the effectiveness of a tailored UP-C/A for this group.

Aims and hypotheses

This study is called the **U**nified **P**rotocol for **C**hildren and **A**dolescents with **M**edical conditions study (The UP-CAM Study). The overarching aim of this study is to adapt and trial the efficacy of the transdiagnostic UP-C/A intervention to reduce symptoms of anxiety and depression in children and young people with CMCs, and to assess the influence of this treatment on functional outcomes. Specific aims are to: (1) adapt the UP-C/A for children and young people with CMCs with input from key stakeholders, (2) pilot the adapted intervention to assess its feasibility, acceptability, and appropriateness, as well as evaluate the trial process (e.g., protocol adherence), (3) assess the efficacy of the UP-C/A in children and young people with CMCs in a RCT, using an intervention and a waitlist control group, (4) examine whether treatment outcomes will be associated with demographic and illness-related factors (e.g., child's age, sex, duration of illness, family burden, socioeconomic status, and parents' psychological distress) [12, 27], and (5) evaluate changes associated with the UP-C/A intervention in these functional domains: adaptive behaviour, HRQoL, sleep, emotional regulation, and self-esteem/self-perception.

We hypothesise that: (1) the adapted UP-C/A intervention will be feasible, acceptable, and appropriate in young people with CMCs, based on findings from the pilot study, (2) eight weeks into the UP-C/A treatment, symptoms of anxiety and depression will be significantly lower in the immediate intervention group compared to the waitlist group, and symptoms will be significantly lower in both groups post-treatment, which will be maintained 3 months post-intervention, (3) UP-C/A treatment outcomes will be associated with demographic and illness-related factors specified in aim 4, and (4) UP-C/A intervention will be associated with positive changes in other functional areas: adaptive behaviour, HRQoL, sleep, emotional regulation, and self-esteem/self-perception.

Methods/Design

Trial approval and registration

The study is registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR 12624000114549; Date: February 23, 2024), and the Universal Trial Number of this study is U1111-1285-0860. Ethics approval has been granted by the Royal Children's Hospital Human Research Ethics Committee (RCH HREC: 90983; Version: 5; Date: May 28, 2024). This trial will be reported in accordance with CONSORT statement [46], and the protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [47].

Trial design

This study uses a RCT design and includes a waitlist control group. We will first adapt the UP-C/A intervention and conduct an internal pilot study ($n = 6$, who are part of the RCT, three for each respective group) to evaluate the feasibility, acceptability, and appropriateness of the intervention for this population.

RCT participants will be randomly allocated to one of two groups: (1) UP-C/A group ($n = 30$) and (2) a waitlist control group ($n = 30$); 1:1 allocation ratio. This is a single-group trial since both groups are children with CMCs experiencing anxiety and depression. Participants in the immediate intervention group will be assessed at: baseline (T1, after trial consent and prior to randomisation), 8

weeks into the intervention (T2), immediately post-intervention (T3), and at 3 months post-intervention (T4). Those in the waitlist group will complete T1, T2 (at the end of their eight-week waitlist period), T3, and T4. The study uses a superiority framework, expecting better outcomes in the immediate intervention group at/up to T2.

Trial setting

Participant recruitment, initial assessment, and follow-up assessments will be conducted within The Royal Children's Hospital (RCH) Clinical Psychology Service, Melbourne, Australia. The service has a state-wide catchment for children and young people with CMCs and provides psychological assessment and evidence-based treatment for those experiencing a range of emotional and behavioural difficulties in relation to a CMC, and their families.

Trial population, pilot, eligibility criteria, consent, and recruitment

The participant selection process is illustrated in Fig. 1.

Population

The RCT participants will be 60 children and young people (8 years to 17 years, 11 months old) who have been referred to the RCH Clinical Psychology Service as outpatients.

Internal pilot study

As stated in aim two, an internal pilot study will assess the feasibility, acceptability, and appropriateness of the adapted UP-C/A, as well as feasibility of the trial processes [48]. The latter will test the recruitment methods, consent processes, randomisation, adequacy of outcome data collection, and protocol adherence. The pilot will involve the first six ($n = 6$) RCT participants, allocated to the immediate intervention ($n = 3$) and waitlist control ($n = 3$) groups, respectively. Some benefits of using this piloting method include maximising the use of time and trial resources and an opportunity to review the study methods to enhance trial succeeds [48, 49]. This method also allows us to include the pilot data in the final analysis. Recruitment for the pilot study will commence after adaptation of the intervention (See Table 1).

Inclusion criteria

Participants must meet the following inclusion criteria: **a**) have a CMC, defined as any medical condition where the child/young person has regular appointments or is seen every 6 months at the RCH Clinical Psychology Service, and has anxiety and depression symptoms associated with their CMC or impacting their medical condition (e.g., treatment adherence). Examples of CMCs include asthma, congenital heart disease, diabetes, epilepsy, brain injury, stroke, inflammatory bowel disease, juvenile idiopathic arthritis, and sickle cell disease, **b**) score above the high-risk clinical range (≥ 65) on a subscale or the total score on the Revised Child Anxiety and Depression Scale (RCADS), to indicate clinically concerning levels of depression and/or anxiety (either parent-report/self-reported), and **c**) the child or young person and one parent are required to be fluent in the English language.

Exclusion criteria

Potential participants meeting any of the following criteria will be excluded (**a**) having a CMC where significant medical deterioration is expected or being in palliative care; (**b**) if taking psychotropic medication, not having a stable dose for the 8 weeks prior to starting the study, (**c**) children/young people with co-occurring somatisation, eating disorders, bipolar disorder, recent psychiatric hospitalization, or severe suicidal ideation or treatment-interfering substance abuse, or (**d**) significant intellectual disability where the clinician expects that modifications to the UP-C/A protocol would be required prior to administration.

Sample size justification

This study aims to include 30 participants each in the immediate intervention and waitlist control groups. To attain a high effect size (Cohen's $d = 0.85$) on the RCADS, a sample size of 23 is required in each group to detect differences between the intervention and waitlist control groups (calculated using G*Power [50], with an alpha level 0.05 and 80% power). With 20% expected participant loss due to withdrawal or non-completion (completing less than 8 session), the study is sufficiently powered with a sample size of 30 participants per group.

Recruitment: intake interview

As shown in Table 1, recruitment for the pilot is scheduled to begin in August 2025. Families attending The RCH Clinical Psychology Service for assessments will be asked to complete a phone intake interview with a psychologist, which will comprise a standard intake screening checklist and the study inclusion and exclusion criteria. Electronic Medical Records of potential participants will be checked to verify exclusion criteria **c** (i.e., diagnosis of eating disorders, significant intellectual disability-(suspected IQ < 70) etc.). If the child/young person is found eligible based on the study inclusion criteria, the family will be asked if they consent to their child's details being passed onto the research team and whether they would like to receive more information about the study. Enrolment will be in two stages: the eligibility screening and trial enrolment stages.

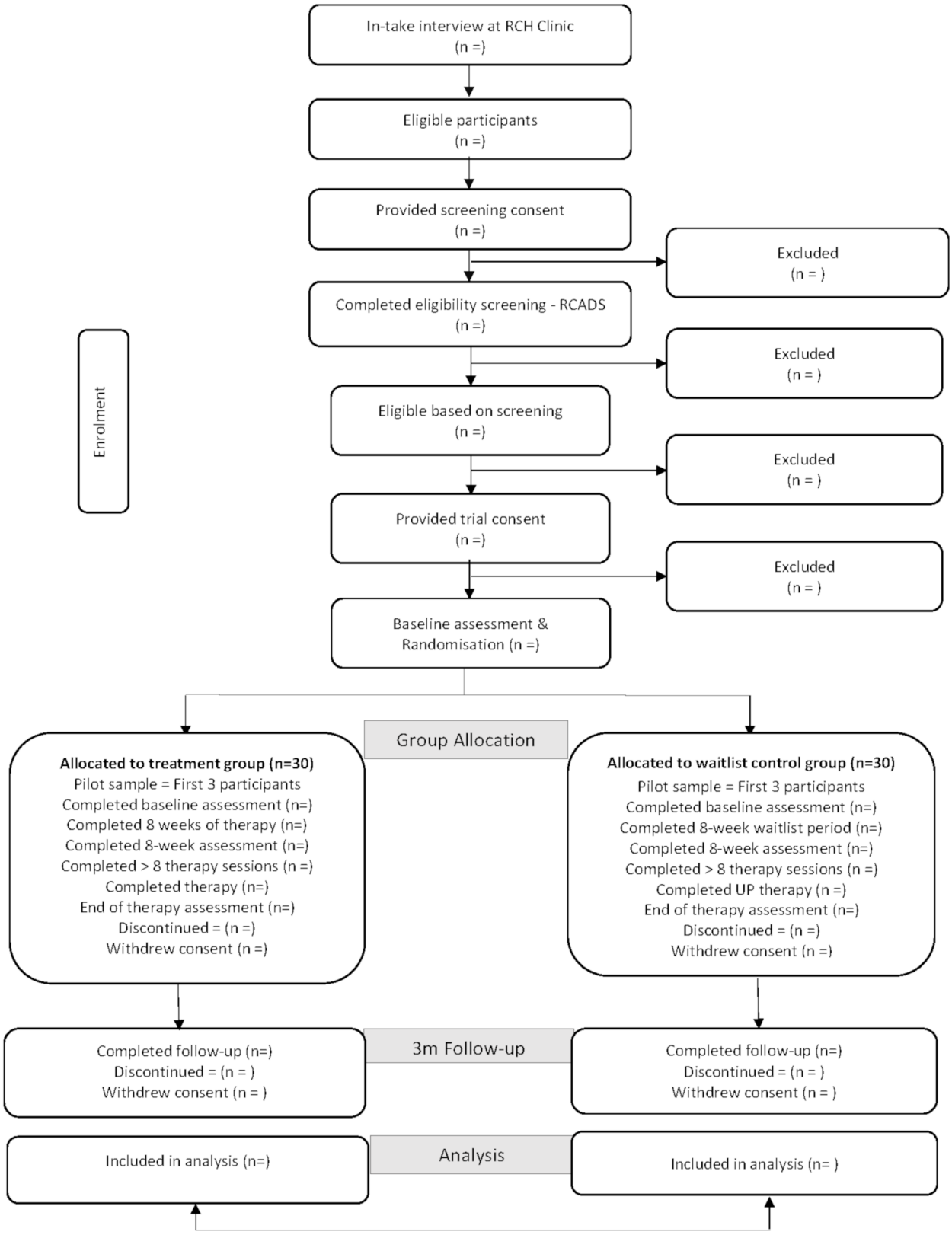

Fig. 1 CONSORT Chart. Pilot study participants will be part of the total trial sample. The 8-week assessment will be conducted after participants complete 8 weeks of the therapy, which will coincide with the end of the waitlist period. ***Discontinuation*** from trial intervention - where a participant stops the trial intervention but should continue follow-up procedures and assessments. ***Withdrawal***– withdrawal of consent for all trial participation by the participant or legal guardian (the participant may withdraw consent prior to or during the trial intervention phase or during follow-up)

Table 1 Trial timelines

	PRE-TRIAL		**TRIAL PERIOD**					
	Ethics, Stakeholder Engagement, & Intervention Adaptation	**Internal Pilot**	**Enrolment & Allocation to Intervention**	**Post-allocation**				
TIME POINTS	Pre–trial 07/24 – 07/25	Pre–trial 08/25 – 03/26	t_0 (04/26– 12/26) enrolment	t_1 baseline	t_2 8 weeks into treatment	t_3 Immediate post–treatment	t_4 3 months post–treatment	t_x (05/27 –03/28)
ETHICS APPROVAL: Obtain ethics approval	X							
Lived experience input	X							
Intervention adaptation		X						
ENROLMENT:								
Intake Interview stage			X					
Eligibility screening stage			X					
Trial stage			X					
Randomisation & allocation			X					
INTERVENTION GROUPS:								
UP-C/A Intervention group				X	X	X	X	
UP-C/A waitlist group				X*	X	X	X	
ASSESSMENTS:								
Baseline assessment (t_1)				X				
8-week assessment (t_2)					X			
Endpoint assessment (t_3)						X		
3 months-post intervention (t_4)							X	
ANALYSIS AND WRITE-UP								X

Note: *T2 assessment for the waitlist group will be conducted at the end of the 8-week waitlist period

Recruitment: eligibility screening

At the eligibility screening stage, families identified as interested in the study will receive a Participant Information Statement and Consent Form (via post or email), with which they can consent to have their child/young person included in the study. Separate versions of the Participant Information Statement and Consent Forms will be provided for parents or guardians, adolescents, and younger children (Child Information Sheet), with each using language that is developmentally appropriate for the target group. Parents will provide written consent for all participates. All children and young people under 18 years of age who are deemed sufficiently mature (i.e., have the cognitive and emotional capacity to understand research participation and provide informed assent) to provide written consent will be asked to do so. Children or young people who cannot provide written consent can provide verbal agreement after reading the Child Information Sheet and having the study explained to them at a developmentally appropriate level by a study team member.

Families who consent to have their child/young person screened for the study will be emailed the RCADS to help determine if the child/young person meets the criteria for anxiety or depression symptoms. Parents and adolescents (12–18 years) will complete this questionnaire online, for 5–10 min, via REDCap, a safe data collection and management tool [51]. Young people who show clinically concerning symptoms of anxiety and/or depression (i.e., score ≥ 65 on the any subscale of the RCADS) and who meet the study inclusion criteria will be included in the randomisation phase of the study.

Decisions about eligibility for the study will be communicated to the family within 7 days of completing their intake assessment and the RCADS. If the child/young person does not meet the criteria or information arises in the interview that would exclude them, the study team will facilitate the appropriate referral. Families who do not respond to the study invitation after two weeks will be followed-up via a phone call/text. Individuals who decline participation or are deemed ineligible after screening will receive usual care from The RCH Clinical Psychology Service, provided they meet the service's eligibility criteria.

Recruitment: trial stage

Children or young people who meet the eligibility screening criteria will proceed to the trial stage of the study, where they will be randomised into either of the study groups.

Randomisation and blinding

Clinicians conducting assessments and delivering the therapy will be blind to group allocation. Randomisation will be implemented using sequentially numbered sealed envelopes and managed by an independent researcher not involved in recruitment or intervention delivery. This method will be used to randomly assign participants to the UP-C/A intervention ($n = 30$) and the waitlist control ($n = 30$) groups, who will receive the intervention immediately and 8 weeks after enrolling in the study, respectively. During the waitlist period, the waitlist control group will be monitored fortnightly by a clinician via telephone check-ins [13] to limit risk of missing any clinically concerning incidents in participants during this period. Any concerns (i.e., mental health or risk-related) will be flagged with a designated psychologists at the RCH Clinical Psychology Service. All assessors will be blind to group assignment for all assessment time points beyond baseline.

The intervention, adaptation, and stakeholder engagement

The UP-C/A intervention

The current project will adapt the UP-C/A [13, 52] for use in children and young people with CMCs. Study participants between 8 and 11 years and 12–17.11 years will receive the child (UP-C) and adolescent (UP-A) versions of the intervention, respectively. Each version contains common treatment elements, tailored to target core dysfunctions underlying emotional disorders [12]. The child version (UP-C) includes 15 sessions [13], with corresponding parent/caregiver components for each session that focus on helping caregivers identify and replace emotional parenting behaviours (e.g., criticism and inconsistency) with helpful parenting behaviours (e.g., empathy and healthy emotional modelling). It is divided into five modules or CLUES skills - "Consider How I Feel", "Look at My Thoughts", "Use Detective Thinking and Problem Solving", "Experience My Emotions", and "Stay Healthy and Happy". The adolescent version (UP-A) comprises eight core modules, with an optional parent module (on parenting the emotional adolescents), each of which is designed to be flexible in length to accommodate patient heterogeneity [13].

Registered psychologists will deliver the intervention on a one-on-one basis. The psychologists will be trained on the UP-C/A and supervised fortnightly by CB, a Senior Clinicians and a certified UP-C/A trainer. Therapy sessions will be completed weekly in the first 8 weeks to match the waitlist period [13] and then weekly/fortnightly for the remaining sessions for flexibility. Variations in this schedule will be documented and adjusted for statistically. It is expected that participants will complete a minimum of 8 sessions and a maximum of 21 sessions, depending on their individual needs, as determined by the psychologist delivering the therapy in consultation with the study Clinical Supervisor (CB). In

line with other UP-C/A trials, participants completing 8 or more sessions will be considered "treatment completers" [11, 13]. Sessions will be administered both face to face and online (via RCH telehealth), with participants required to attend a minimum of three face-to-face sessions. The immediate follow-up assessment appointment will be scheduled once the intervention is completed.

Stakeholder consultations for study design, intervention adaptation, and delivery

As illustrated in Fig. 2, we will consult stakeholders to inform the adaptation of the UP-C/A for this population. The stakeholders will include lived experience groups, as well as clinicians and medical professionals working with this population at the RCH (e.g., psychologists and physicians). The lived/living experience groups will include children (8–11 years old, $n = 5$) and adolescents (12years–20years, $n = 7$) with a CMC, young adults who experienced CMC in childhood ($n = 8$), and parents/guardians of children and young people with a CMC ($n = 10$). They will be clients of the RCH Clinical Psychology Service or members of the RCH Lived Experience Network and will be invited to join this group via official channels provided by the RCH (e.g., RCH's Facebook page). We will ensure that this group is diverse and representative of the target population (e.g., by age, gender). Separate consultation sessions will be held for each stakeholder group and interested participants will be asked to provide written or verbal consent to join the groups. Adult lived experience participants (i.e., 18 + years) will be compensated financially using rates determined by the RCH Lived Experience Network, while children and adolescents will be offered a gift voucher. Stakeholders will be invited to attend three consultation sessions: (1) To gather feedback on the research design, intervention content, and intervention delivery methods. (2) To explain how their feedback was incorporated and solicit their final feedback on the adapted program. (3) To learn from their reflections on the study findings at the end of the RCT.

Feedback can be provided via a group consultation meeting, one-on-one conversation, or in writing. The consultation sessions will be co-facilitated by members of the research team and a Lived Experience Facilitator (JW). Suggestions/adaptations arising from these consultation sessions will be submitted for ethics approval prior to commencing the RCT.

Intervention adaptation

The stakeholder engagement and intervention adaptation process are illustrated in Fig. 2. It is anticipated that adaptions may include modifying examples/scenarios provided in the UP/C-A to medically specific examples that are more relatable to children and young people with CMCs. Suggestions around the mode and frequency of intervention delivery and assessment targets will also be considered. The adaptation aims to enhance accessibility, relatability, engagement, and appropriateness of this intervention for children and young people with CMCs.

Adaptions will be based on recommendations from the stakeholders (i.e., clinicians, medical professionals, and people with lived experience of CMCs). It will be guided by the Iterative Decision-making for Evaluation

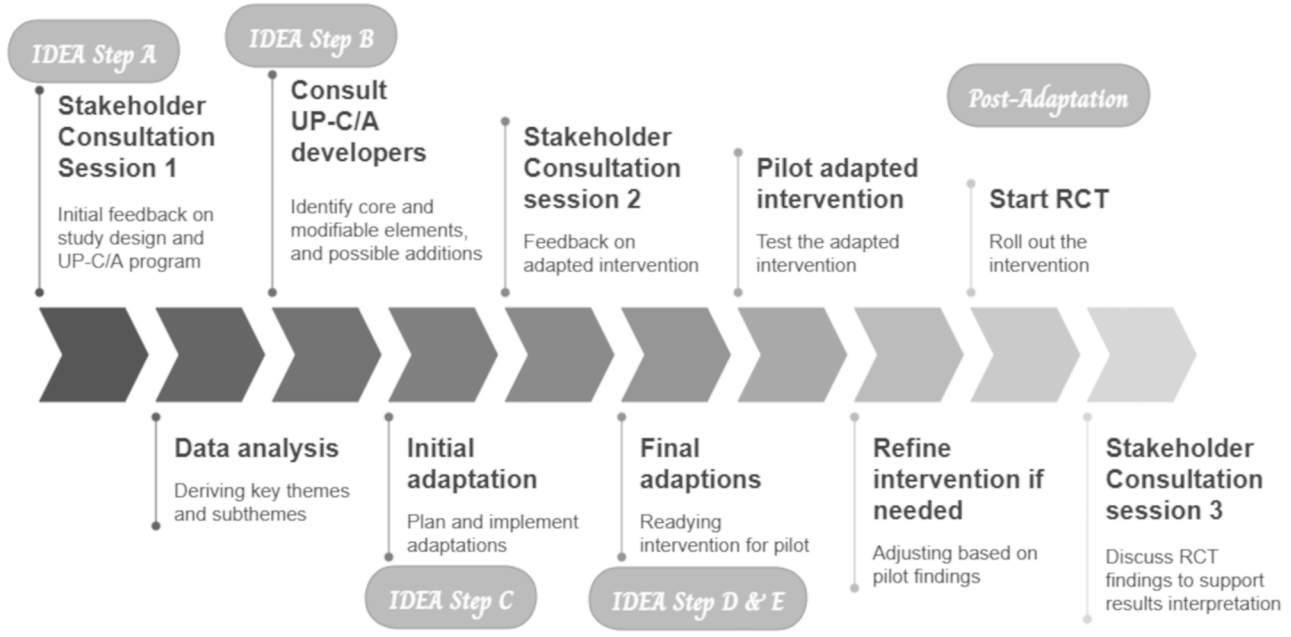

Fig. 2 Stakeholder consultation and intervention adaptation process. This process is based on an adapted version of the Iterative Decision-making for Evaluation of Adaptations (IDEA) framework, depicted here to include Steps A to E [53]

of Adaptations (IDEA) framework (adapted version), which helps define key decision points in the adaptation process while accounting for the iterative nature of the process [53]. Based on this framework, we will: consult key stakeholders (i.e., clinicians and people with lived experience of CMCs) to establish the need to adapt the UP-C/A for young people with CMC (**Stakeholder Session 1 - IDEAS Step A**); consult the UP-C/A developers to identify core and modifiable elements of the UP-C/A, as well as consider additional modules needed per the stakeholders' recommendations (**Consult UP developers - IDEAS Step B**); adapt the UP-C/A in consultation with the Lived Experience Facilitator (JW) and the UP-C/A developers to address key barriers and modifications suggested. Share the adapted intervention with the Stakeholders for their final input (**Initial adaptation** & **Stakeholder Session 2 - IDEAS Step C**); Finalise the adaptations and pilot the adapted intervention to assess its feasibility, acceptability, and appropriateness ($n = 6$) (**Final adaptations & Pilot - IDEAS Step D**, **E**); and refine adapted intervention based on findings from the prior study, in preparation for the RCT. Adaptations made will be reported using the Framework for Modification and Adaptations– FRAME, a tool used to monitor and record proactive and reactive adaptations [54].

Therapist training and treatment fidelity

Psychologists delivering the intervention will complete training from an experienced UP-C/A therapist (CB), whose training will be based on materials created by the UP-C/A developers. To maximize the psychologists' adherence to the treatment protocol, they will participate in fortnightly clinical supervision sessions with CB and the intervention developers (SK). 15% (15%) of treatment sessions will be recorded with participant and parental permission and reviewed by the Research Coordinator to ensure the protocol is adhered to. A study-developed checklist will be used to evaluate each therapy session, and the entries will be scored to provide a quantitative measure of treatment fidelity (Table 1).

Strategies to improve engagement/reduce attrition

We will contact waitlist participants fortnightly via phone calls during the 8-week waitlist period to maximise engagement of families in the trial and reduce attrition. Participants will also be contacted monthly during the 3-month follow-up period (i.e., after the immediate follow-up assessment) to reduce attrition.

Trial measures and assessments procedures

Assessment timepoints are illustrated in Fig. 1, and Table 1 presents the schedule for enrolment, intervention, and assessments. Participants in the immediate intervention group will be assessed at: T1 (after trial consent and prior to randomisation), T2, T3, and T4. Those in the waitlist group will complete T1, T2 (at the end of their eight-week waitlist period), T3, and T4. Except for the face-to-face assessments specified below, all assessments will be completed online, through REDCap and will take 70 to 90 min. Surveys can be completed on phones/iPad/laptop at participant's own convenience.

Face-to-face assessments will be conducted at T1 and T3, using the MINI-KID [55] and the Children's Global Assessment Scale (to determine general functioning). A trained diagnostic interviewer will administer all applicable sections of the MINI-KID. Parents will be required to attend the RCH Clinical Psychology Service with their child/adolescent for these assessments. The duration of this session will be determined by the responses provided to the core MINI-KID items and can take between 15 to a maximum of 50 min.

Table 2 specifies the measures used at each timepoint of this study.

Trial outcomes

Primary outcome

The primary outcome of this study will be the extent of change in anxiety and depression symptoms in the intervention vs. waitlist control groups, which will be evaluated (T2, T3, T4) using the parent-rated and child-rated scores (total and subscales) on the RCADS.

Secondary outcomes

There are two secondary outcomes in this study.

(a) Feasibility, acceptability, and appropriateness of the UP-C/A intervention. These will be evaluated from the perspectives of parents and the clinician, using the Feasibility of Intervention Measure, Acceptability of Intervention Measure, and Appropriateness of Intervention Measure. A study-designed feasibility measure will also be administered to parents and adolescents. See Table 2.

(b) Identifying functional changes associated with the UP-C/A intervention. Self-esteem (assessed with the Harter Self Perception Measure), HRQoL (from the Child Health Utility- 9D), adaptive behaviour (using the Adaptive Behaviour Assessment Systems), sleep (using the Sleep Disturbance Scale for Children), and emotional regulation (assessed with the Emotional Regulation Questionnaire for Children and Adolescents).

Anticipated risks and management strategies

No side effects or physical, legal, or social risks are anticipated for this trial. Families may incur some financial/economic risks (e.g., time spent to participating and cost of travel for the in-person assessment) and participants

Table 2 Study measures and assessment details

Construct	Measure	Details	Completer	Timepoints administered
Clinical and demographic information	Study-designed measure and medical records	Clinical and demographic information will be collected from both participants and parents using a study-designed demographic questionnaire and from the participant's electronic medical records. **Duration**: 5–10 min	Parent Child	T1
Anxiety and depression	RCADS	**Items**: 47 **Outcomes**: Six subscales (separation anxiety, generalized anxiety disorder, panic disorder, social phobia, obsessions-compulsions disorder, and major depressive disorder) and overall depression/anxiety score [45] **Clinical cut-off**: = ≥65 **Duration**: 5–10 min	Parent Child	T1, T2, T3, T4
Health-related quality of Life	CHU-9D	**Items**: 9 **Outcome**: Total HRQoL score [51, 52] **Duration**: 5 min	Parent Child	T1, T3, T4
Self-perception	HSPM	**Items**: 36 **Outcomes**: Five concept domains (scholastic competence, athletic competence, social competence, physical appearance, and behavioural conduct) and global self-worth/self-esteem) score [53, 54] **Duration**: 10–15 min	Child	T1, T3, T4
Emotional regulation	EMQ-CA	**Items**: 10 **Outcomes**: Assesses emotional regulation in children and adolescents [55]. The total score will be reported. **Duration**: 5 min	Parent	T1, T3, T4
Sleep disturbance	SDSC	**Items**: 26 **Outcomes**: Six subdomains (disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence, sleep hyperhidrosis) and the total sleep disturbance score [56] **Duration**: 5–10 min	Parent	T1, T3, T4
Psychiatric disorders	MINI-KID	**Items**: Depends on pattern of responses. **Outcomes**: Scores on depressive disorders, suicidality, bipolar disorders, anxiety disorders, obsessive compulsive disorder, posttraumatic stress disorder, alcohol abuse, substance abuse, tic disorders, ADHD, disruptive disorders, psychotic disorders, eating disorders, and pervasive developmental disorders [44] [57] **Duration**: 15–50 min	Child Parent	T1, T3
Feasibility, Acceptability, Appropriateness	FIM/AIM/IAM &	**Items**: FIM/AIM/IAM (4 items each) **Outcome**: Mean scores on the FIM/AIM/IAM [58] **Duration**: 2–3 min	Parent Therapist/Clinician	T2, T3
Feasibility	Study-designed questionnaire	Mean scores on each item of the study-designed acceptability questionnaire. **Duration**: 2–5 min	Parent Child	T2, T3
Treatment Fidelity	Study-designed fidelity measure	Each participant's score and mean group scores will also be evaluated. **Duration**: 3–5 min	Therapist/Clinician	At the end of each therapy session
Global functioning	CGAS	**Items**: 1 **Outcome**: Rates general functioning [59] **Duration**: 2 min	Therapist/Clinician	T1, T3, and at the end of each therapy session
Adaptive Behaviour	ABAS-3	**Items**: 232 **Outcomes**: Three domain scores (conceptual domain, social domain, and practical domain) and a global adaptive composite score [60] **Duration**: 10–15 min	Parent	T1, T3, T4

Table 2 (continued)

Construct	Measure	Details	Completer	Timepoints administered
Family burden	FBI-A	**Items**: 27 **Outcomes**: Rates stress levels in a variety of domains including, child adjustment and behaviour, relationship with spouse, impact on siblings, and relationships with other/extended family [61] **Duration**: 15–20 min	Parents	T1, T3, T4
Parental Psychological Distress	K-6	**Items**: 6 **Outcomes**: Assesses risk of serious mental problems in the last 30 days based on these items: "nervous," "hopeless," "restless or fidgety," "depression," "that everything was an effort," and "worthless" [62] **Duration**: 3–5 min	Parent	T1, T3, T4

Notes: ABAS, Adaptive Behaviour Assessment Systems; ADHD, Attention Deficit Hyperactive Disorder; AIM, Acceptability of Intervention Measure; CAMM, Child and Adolescent Mindfulness Measure; CGAS, Children's Global Assessment Scale; CHU-9D, Child Health Utility- 9D; ERQ-CA, Emotional Regulation Questionnaire for Children and Adolescents; FBI-A, Adapted Family Burden Interview; FIM, Feasibility Intervention Measure; HRQoL, Health-Related Quality of Life; HSPM, Harter Self Perception Measure; IAM, Appropriateness of Intervention Measure; K6– Kessler 6; MINI-KID, Mini-International Neuropsychiatric Interview (Kids version); RCADS, Revised Child Anxiety and Depression Scale; SDSC, Sleep Disturbance Scale for Children. T1 (baseline), T2 (8 week into intervention assessment/end of waitlist period), T3 (immediately post-intervention), and T4 (3 months post-intervention)

may experience some emotional distress from responding to some content during assessment or therapy sessions, since these tap into an individual's emotional experiences. The latter is highly unlikely however, since the assessment measures [56] and the UP-C/A intervention [13, 52] are validated and extensively used in children. In addition, any emotional distress that arises will be well-managed by the highly trained clinicians. For both participant groups, any additional interventions received, or concurrent medical events/treatment required during their participation in the study will be documented.

Data management

Assessment data will be collected in-person (by psychologists within the RCH Clinical Psychology Service) and online via REDCap. Each participant will be allocated a unique study identification number upon enrolment in the study. Data collected via REDCap will be through Murdoch Children's Research Institute's (MCRI) REDCap account and will be safely stored behind a firewall. All study-related data will be stored using safe physical and digital data storage systems provided by the MCRI and RCH. At the end of the study, each participant will receive a personalised account of their outcomes in the study. This will be communicated using the Final Study Letter and will be sent to participants via email/post.

A detailed Data Management Plan has been prepared for this RCT, describing how data will be collected, coded, stored, used, and managed. The Data Safety Management Board will be established for this trail and will include a chairperson with trial management/governance experience, the Principal Investigators, a statistician, psychologists, and a medical doctor. The board will be responsible for safeguarding the interests of trial participants, assessing trial progress, and the safe delivery of the interventions during the trial. They will review the plan for the collection of data before the first patient is enrolled in the trial. Following their initial meeting, the board will meet every 12 months to review data quality, recruitment and retention outcomes, trial conduct, and trial safety.

Data analysis

Data will be cleaned and analysed in SPSS. Prior to each analysis, data will be checked to ensure adherence to all statistical assumptions (e.g., normality, linearity, homoscedasticity). Little's Missing Completely at Random Test (MCAR) will be used to determine pattern of missing data, and missing values will be managed based on methods compatible with respective statistical models (e.g., multiple imputation, mean substitution). Descriptive statistics will be generated for baseline (demographic and clinical) characteristics for each group. Between-group comparisons on baseline characteristics will be

carried out using *t*-tests, chi-squared tests, and Mann-Whitney U tests (as applicable).

Descriptive statistics will be used to evaluate the feasibility, acceptability, appropriateness, and preliminary efficacy of the adapted UP-C/A, based on pilot data (Hypothesis 1). To evaluate efficacy of the UP-C/A intervention in the RCT (Hypothesis 2), intention-to-treat analysis will be conducted. Independent samples t-tests will be used to assess mean group differences in RACDS total depression/anxiety scores at T2, and paired sample t-tests will be used to determine whether post-treatment (T3) changes are maintained at T4. In addition, dichotomised RCADS scores (T2 only in the intervention group, T3, T4) will be used to distinguish between participants (Chi-squared tests): "remission" (i.e., individuals achieving nearly a symptom-free status; Cut-off score, ≤ 60 on any subscale of the RCADS) and "response" (i.e., individuals achieving a clinically meaningful improvement relative to baseline; Cut-off score, ≥ 60 on any subscale of the RCADS).

For hypothesis 3, multiple linear regression models will be used to explore whether these demographic and health-related factors are associated with the UP-C/A treatment outcomes (i.e., anxiety and depression): child's age, sex, duration of illness, family burden, socioeconomic status, and parents' psychological distress [12]. Hypothesis four will involve the use of linear mixed models evaluating functional gains associated with the UP-C/A treatment at T2 (only the intervention group), T3, and T4 for: self-esteem, adaptive behaviour, health-related quality of life, emotional regulation, and sleep.

For all analyses, means, standard deviations, *p*-values, confidence intervals, and effect sizes will be reported, where available.

Trial management

The Sponsor Investigator/Principal Investigator (LC) will oversee the project. They will be responsible for managing all major project-related communication, both in, and outside the research team (e.g., public enquiries). A Trial Management Committee will provide oversight in this trial and will include the key research team (i.e., Principal Investigators and Research Co-ordinator), an independent Psychologist, and an Independent medical doctor. They will meet every 4–6 months to review progress of the trial.

The Principal Investigator will also communicate any important protocol deviations/adverse events to all study investigators and relevant offices (e.g., RCH Ethics Committee). Research team members will ensure that such events are recorded and reported to the Principal Investigator within 24 h of becoming aware of the event, and the Principal Investigators will ensure such events are reported to the other investigators and RCH HREC. The Risk Management Plan for this trial details procedures for detailing with such events and can be accessed by contacting the corresponding author. They will also meet with the project team periodically to discuss study procedures, problems that arise, and to monitor adherence to the protocol.

Trial dissemination and translation plan

Results from this study will be published in international peer review journals and conferences/conference proceedings. The data will also be presented in academic gatherings including local and international conferences, as well as internal meetings such as department meetings, staff conferences within MCRI and RCH. At the end of the project (i.e., following data collection and analysis), each participant will be provided with a Final Study Letter, which will explain the overall study findings. Each participant can also opt to receive a letter that outlines their individual outcomes in the study. These letters will be sent via email/post.

Discussion

This RCT will provide valuable evidence on the efficacy of the UP-C/A in children and young people with CMCs who present with anxiety and depression symptoms. If found to be feasible, acceptable, appropriate, and efficacious, the UP-C/A could be adopted for use in public health settings and beyond to help improve emotional disorders in this population. Such an outcome would be very beneficial to improving mental health prognosis in this paediatric population with CMCs who are at an increased risk of emotional disorders yet have limited access to tailored evidence-based interventions [18].

UP programs are more beneficial compared to single-diagnostic therapies since they can treat both anxiety and depression and can be flexibly implemented based on the young person's needs [18]. Although previously found feasible and effective in children and adolescents presenting with anxiety and depression symptoms [13, 16, 27], and in one study involving children with chronic pain [32], this will be the first trial to extensively assess the UP in children and adolescents with CMCs. For this reason, the project is carefully tailored to this CMC population by adapting some elements of the original UP-C/A to enhance engagement in this group of young people, with some of the methodological considerations explained below.

Methodological considerations

The following methodological concerns have been considered in this project.

Adapting the UP-C/A for children and adolescents with CMCs

To improve engagement, accessibility, relatability, and appropriateness of the UP-C/A for the target population, we are consulting clinicians and lived experience groups, as well as the developer of the UP-C/A to inform the adaptation process.

Addressing potential power imbalance in lived experience groups

To limit the risk of power imbalances in the lived experience groups, separate sessions have been arranged for different age groups (e.g., young adults and adolescents) to ensure participants feel comfortable and safe sharing their perspectives. Additionally, we have employed a Lived Experience Facilitator (JW), who will co-develop and co-facilitate the adaptation workshops with the research team.

Use of a waitlist control group

This study uses a waitlist control group instead of a no treatment or placebo control group since it will be unethical to deny participants access to intervention in the context of this study. Using this type of control group will provide an untreated comparison for the active experimental group to help quantify treatment effects, while also giving the control group access to the intervention [57]. The decision to limit the waitlist period to 8 weeks is ethically considerate and is the standard waitlist period in some prior RCTs targeting young people with anxiety [13, 58]. Although the waitlist control group method is said to sometimes cause people to stall in their personal efforts to change behaviour [59] and overestimate treatment effects, our short waitlist period (i.e., 8 weeks) and regular contact with this group during the waitlist period are expected to mitigate this effect.

Use of intention-to-treat analysis

By including all participants originally randomised to the respective groups in our analysis, we will be preserving the prognostic balance afforded by randomization and minimize any risk of bias that may be introduced by comparing groups that differ in prognostic variables [60].

Conclusion

The study will employ gold-standard trial methodology and assess the feasibility, acceptability, appropriateness, and efficacy of an adapted UP-C/A intervention with the aim of improving anxiety and depression outcomes in children and adolescents with CMCs. The findings from this RCT are expected to provide the much-needed evidence for use of UP-C/A interventions in children with CMCs who present with anxiety and depression symptoms. We also expect to find sustained improvements in other functional domains, to further support the adaptation of this intervention. Finally, the predictors associated with UP-C/A outcomes in this trial can inform treatment decisions towards better personalised care in these children and adolescents with CMCs.

Abbreviations

ABAS	Adaptive Behaviour Assessment Systems
ADHD	Attention Deficit Hyperactive Disorder
AIM	Acceptability of Intervention Measure
ANOVA	Analysis of Variance
ANZCTR	Australian and New Zealand Clinical Trials Registry
CGAS	Children's Global Assessment Scale
CHU-9D	Child Health Utility- 9D
CMCs	Chronic Medical Conditions
ERQ-CA	Emotional Regulation Questionnaire for Children and Adolescents
FBI-A	Adapted Family Burden Interview
FIM	Feasibility Intervention Measure
HRQoL	Health-related quality of life
HSPM	Harter Self Perception Measure
IAM	Appropriateness of Intervention Measure
IQ	Intelligence Quotient
K-6	Kessler 6
MCAR	Missing Completely at Random Test
MINI-KID	Mini-International Neuropsychiatric Interview (Kids version)
RCADS	Revised Child Anxiety and Depression Scale
RCH	Royal Children's Hospital
RCH HREC	Royal Children's Hospital Human Research Ethics Committee
RCT	Randomised Control Trial
SDSC	Sleep Disturbance Scale for Children
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
UP	Unified Protocol
UP-C/A	Unified Protocol for the treatment of emotional disorders in children and adolescents
T1-T1	Timepoints 1 to 4: baseline assessment,8-week assessment, immediately post-intervention assessment, and 3 months post-intervention assessment, respectively

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Author contributions

Louise Crowe, Edith Botchway-Commey, and Claire Burton are co-principal investigators and contributed to the conception of the study design, management of the day-to-day study activities, and the preparation and revision of the manuscript. Jill Ehrenreich-May, Sarah Michelle Kennedy, Carmen Pace, James Williams, Zeffie Poulakis, and Vicki Anderson contributed to the conception of the study design and revision of the manuscript.

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Data availability

The data for this study may be available on request.

Declarations

Ethics approval and consent to participate

Ethics approval for this study was granted by the Human Research Ethics Committee of the Royal Children's Hospital (RCH), Melbourne (HREC 90983; Version: 5; Date: May 28, 2024). The study will be duly conducted in adherence

with this approved protocol. Written/verbal informed consent for participation in the study will be obtained from all participants prior to their involvement.

Consent for publication
Not applicable. Individual data is not reported in this protocol paper.

Competing interests
The authors declare no competing interests.

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