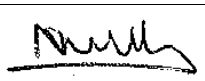
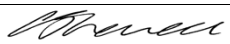
Primary Care Clinical Trials Unit

STATISTICAL ANALYSIS PLAN

Child Anxiety Treatment in the context of COVID-19 (Co-CAT):

Enabling Child and Adolescent Mental Health Services (CAMHS) to provide efficient remote treatment for child anxiety problems

Version 3.0 1st September 2022

	NAME	TITLE	Signature	Date
Written by:	Nicola Williams (version 1.1 onwards)	Senior Trial Statistician		1st September 2022
Reviewed by:	Ly-Mee Yu	Lead Trial Statistician		20th Sept 2022
Approved by:	Cathy Creswell	Chief Investigator		19th September 2022

Version History

Version:	Version Date:	Changes:
0.1	30 Sept 2020	Original
0.2	08 October 2020	Responded to reviewer comments by JM
0.3	27 October 2020	Responded to comments by CC
0.4	09 November 2020	Minor updates
0.5	13 November 2020	Updated with comments from CC and JM
0.6	17 November 2020	Updated with comments from CC
0.7	18 November 2020	Updated with comments from JM
0.8	20 November 2020	Clean version
1.0	01 December 2020	Finalised for sign off.

1.1	14 July 2021	Updated to incorporate changes to protocol (now based on v2.0 of protocol) – specifically minimisation variables used in randomisation Add derivation of outcome measures based on questionnaires
1.2	2 November 2021	Updated and removed comments following meeting with Lucy Taylor and Cathy Creswell. • Addition of time windows for inclusion in primary and sensitivity analyses • Removal of t scores 2.1.2.2.1 • Change 2.1.2.5 to 7 itmes, not 9 • Change per protocol to modules 0-4 not 0-3
1.3	10 March 2022	Update to derivation of SCAS-P-8 (section 2.1.2.2.2) following review by Lucy Taylor
2.0	10 March 2022	Finalised for sign off
2.1	1st September 2022	Updated power calculation to be in line with version 2.3 15th July 2022 of protocol (Sample Size Determination updated to reflect sample size requirements from just 90% power to both 80% and 90% power)
3.0	1st September 2022	Finalised for sign off

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1 INTRODUCTION

1.1 PREFACE

Chief Investigator: Professor Cathy Creswell

Trial Statisticians: Dr Ly-Mee Yu, Dr Victoria Harris

This SAP supports version 2.3 of the protocol dated 15th July 2022.

1.2 PURPOSE AND SCOPE OF THE PLAN

This document details the proposed analyses of primary and secondary objectives for the Child Anxiety Treatment in the context of COVID-19 (Co-CAT) study. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis nor to prohibit accepted practices, but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The statistical analysis plan will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by the journal editors or referees will be considered carefully, and carried out as far as possible in line with the principles of the analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial.

1.3 TRIAL OVERVIEW

More than a quarter of the population have an anxiety disorder at some point during their life and half of these people first experience an anxiety disorder by the age of 11 years (Kessler et al., 2005). Anxiety disorders in childhood often continue into adolescence and adulthood and put these children at increased risk for other serious mental health disorders and impaired quality of life in adulthood (Copeland, Angold, Shanahan, & Costello, 2014).

Cognitive behaviour therapy (CBT) for children with anxiety disorders works well (James, James, Cowdrey, Soler, & Choke, 2013), but only a minority of children with anxiety disorders access treatment (Green, McGinnity, Meltzer, Ford, & Goodman, 2005; Merikangas et al., 2011). Improving treatment efficiency further could enable more families to access effective treatment when they first need it. Online delivery of parent-guided treatment offers a means to do this by substantially reducing the amount of therapist contact time needed. Delivering treatment online also has the potential to increase access to families who may experience barriers to accessing traditional treatment approaches.

We have worked in collaboration with families, NHS clinicians and a tech-company to co-design an online version of our parent-guided treatment for child anxiety disorders called OSI (Online Support and Intervention for child anxiety). OSI comprises a parent website, accompanying therapist case management system, and accompanying child game app (see *OSI Overview and Screenshots* document). Modules are supported by 7 x weekly 20-minute telephone sessions between the parent and a therapist and a review session 4 weeks after the final treatment session).

Importance in the context of COVID-19

The Health Innovation Network (Health Innovation Network South London, 2020) highlighted that children with existing anxiety issues are a high risk population during the COVID-19 pandemic, and our UKRI funded Co-SPACE study (CUREC R69060/RE010) that has been tracking child and adolescent mental health throughout the pandemic has identified high levels of fear and worry about COVID-19 among children.

OSI provides a potential means to address the current challenges that CAMHs face in meeting the needs of children with anxiety problems and their families; it can be delivered as intended despite social distancing measures and is sufficiently flexible to address COVID-19 specific fears/worries. It has not yet been subject to systematic evaluation and we do not know whether outcomes are as good as those CAMHS are currently achieving and whether OSI enables further efficiencies.

Aims

The proposed research will evaluate the clinical and cost-effectiveness of OSI with therapist support for the treatment of child anxiety compared to 'COVID-19 treatment as usual' (C-TAU) in CAMHS throughout the next phases of the COVID-19 pandemic. Further aims are to explore the trajectory of change as reported within the OSI platform, to inform further developments, and to understand therapists' and parents' experiences of treating child anxiety (across both arms) in the current context to maximise learning to (a) enable rapid implementation of remote treatment delivery in CAMHS in any subsequent periods of social distancing, and (b) maintain the use of online platforms (such as OSI) in CAMHS when 'normal service' resumes.

If successful, the research will provide:

1. A solution for efficient psychological treatment for child anxiety disorders while social distancing (for the current context and future pandemics);
2. An efficient means of treatment delivery as 'normal service' resumes to enable CAMHS to cope with the anticipated increase in referrals when social distancing measures are relaxed and schools re-open;
3. A demonstration of rapid, high quality evaluation and application of online interventions within NHS CAMHS to drive forward much-needed further digital innovation and evaluation in CAMHS settings.

The primary beneficiaries will be children with anxiety disorders and their families, NHS CAMHS teams, and commissioners who will access a potentially effective, cost-effective, and efficient treatment for child anxiety problems.

1.4 Objectives

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure** **(if applicable)**
Primary Objective To evaluate the parent-reported clinical effectiveness of OSI+therapist support for the treatment of child anxiety compared to 'COVID-19 treatment as usual' (C-TAU) in CAMHS throughout the next phases of the COVID-19 pandemic.	1) The Child Anxiety Impact Scale- parent report (CAIS-P) captures the degree to which anxiety is interfering in the child and family's life.	26 weeks post-randomisation
Secondary Objectives **(1)** Further assessment of the clinical effectiveness of OSI+therapist support for the treatment of child anxiety compared to 'COVID-19 treatment as usual' (C-TAU) in CAMHS throughout the next phases of the COVID-19 pandemic.	Secondary clinical outcomes: Child reported anxiety interference (CAIS-C), child reported anxiety symptoms (RCADS-C) Parent report on child's anxiety symptoms (RCADS-P, SCAS-8P), overall functioning (ORS), COVID-19 specific worries, and common comorbid emotional and behavioural problems (SDQ-P).	14 weeks post-randomisation 26 weeks post-randomisation

(2) Evaluate the cost-effectiveness of OSI+therapist support for the treatment of child anxiety compared to 'COVID-19 treatment as usual' (C-TAU) in CAMHS	Economic outcomes: Parent quality of life (EQ-5D-5L, parent-self report); and child quality of life (CHU-9D proxy version, i.e. parent-report on child). School attendance (actual school attendance as a percentage of expected school attendance) Therapist logs of time spent on treatment delivery	14 weeks post-randomisation 26 weeks post-randomisation
Exploratory Objectives **(1)** Explore the trajectory of change reported within the OSI arm	Measures used to monitor child outcomes built in to OSI (RCADS-P, CAIS-P, SCAS-8P; ORS; SRS; GBOs)	Weeks 1-7 of OSI treatment
(2) Understand therapist and parents' experiences of treating child anxiety in the current context to maximise learning to (a) enable rapid implementation of remote treatment delivery in CAMHS in any subsequent periods of social distancing, and (b) maintain the use of online interventions (such as OSI) in CAMHS when 'normal service' resumes.	Qualitative interviews with parents and therapists. Therapist experience of treatment questionnaire	14-26 weeks post randomisation End of treatment phase

2 TRIAL DESIGN

We will conduct a two arm, multi-site, randomised controlled non-inferiority trial to evaluate the clinical and cost-effectiveness of OSI with therapist support compared to CAMHS 'COVID-19 treatment as usual' (C-TAU) during the COVID-19 outbreak and to explore parent and therapists' experiences. The study procedure is in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement 2013 (Chan et al, 2013).

2.1 OUTCOMES MEASURES AND THEIR DERIVATIONS

2.1.1 PRIMARY OUTCOME

The Child Anxiety Impact Scale- parent report (CAIS-P). The CAIS-P will be used to determine the extent to which anxiety interferes in the child's life. This measure covers three psychosocial domains (academic, social activities and home/family environments) and consists of 27 items rated on a 4-point scale. In keeping with other trials with pre-adolescent children, we are using a 25 item version of the measure (without two items which ask about boyfriend/girlfriends and dating; e.g. Evans et al (2017) and Thirlwall et al (2013)). An additional 4 'global' items assess overall interference. The CAIS-p will be completed at baseline, and then at 14 and 26 weeks post randomisation by both parent/carer and child. The primary outcome is the CAIS-P at 26 weeks post randomisation.

There are versions for children and parents to complete, both of which have been shown to have good psychometric properties (Langley et al., 2014; Langley, Bergman, McCracken, & Piacentini, 2004). The Child Anxiety Impact Scale- child report (CAIS-C) will be analysed as a secondary outcome.

Derivation

Each item is scored on a 4-point Likert scale ("0" not at all, "1" just a little, "2" pretty much, "3" very much). A total score sums the scores of the first 25 items, giving a possible range of 0 to 75.

Missing data for individual questions can be handled by prorating the remaining items to get a total score. This can be done if at least 75% of items have been completed. If more than 75% are missing the total will be set to missing.

A total score for the 4 global items (questions 28-31) will be obtained, with a possible range of 0-12. As above, if at least 75% of the questions have been answered, the total score can be obtained by prorating the remaining items. If more than 75% are missing the total will be set to missing.

2.1.2 Secondary outcomes and Their Derivations

2.1.2.1 Child Anxiety Impact Scale

The Child Anxiety Impact Scale- child report (CAIS-C) covers the same domains as the CAIS-P and will be completed at the same time points as the CAIS-P.

Derivation

The Child Anxiety Impact Scale – child report score is calculated in the same way as for the parent report.

2.1.2.2 Symptoms of Child Anxiety

2.1.2.2.1 Revised Child Anxiety and Depression Scale-Child and Parent versions (RCADS-c/p).

The RCADS-c/p are routinely used within CAMHS. It is a 47-item questionnaire, with corresponding child-report and parent-report versions that assess symptoms of separation anxiety disorder, social anxiety disorder, generalized anxiety disorder, panic disorder, obsessive compulsive disorder and major depressive disorder. Responders rate how often each item applies on a 0 ('never') to 3 ('always') scale. The RCADS-c/p have been shown to have robust psychometric properties in children from age 7 (Chorpita, Moffitt, & Gray, 2005; Ebesutani, Bernstein, Nakamura, Chorpita, & Weisz, 2010). RCADS-c/p will be completed at baseline, and then at 14 and 26 weeks post randomisation by both parent/carer and child.

Derivation

Each of the 47 items is scored on a 4-point Likert scale ("0" never, "1" sometimes, "2" often, "3" always). Question 48 is required for the SCAS-8P only.

Two scores will be obtained:

- A total score for anxiety, which sums the scores for all except major depression (possible range 0 to 111)
- A total overall score which sums scores of all items, giving a possible range of 0 to 141.

These will be presented as raw scores and will not be converted to t-scores.

Disorder/Syndrome	Related Items
Social Anxiety	4, 7, 8, 12, 20, 30, 32, 38, 43
Panic Disorder	3, 14, 24, 26, 28, 34, 36, 39, 41
Major Depression	2, 6, 11, 15, 19, 21, 25, 29, 40, 47
Separation Anxiety	5, 9, 17, 18, 33, 45, 46

Generalized Anxiety	1, 13, 22, 27, 35, 37
Obsessive-Compulsive	10,16, 23, 31, 42, 44

Missing data for raw scores can be handled by prorating the remaining items. It is recommended that the total anxiety score can have up to 10 missing items, but only if each subscale has no more than 2 missing; and the total anxiety and depression score can have up to 12 missing items, but only if each subscale has no more than 2 missing items. To estimate the scale score, take the sum of the completed items within that scale and divide that by the number of items completed, then multiple by the total number of items in that scale, and then round the result.

2.1.2.2.2 Brief Spence Children's Anxiety Scale-Parent Version (SCAS-P-8).

The SCAS-P-8 is a brief version of the Spence Children's Anxiety Scale (Reardon, Spence, Hesse, Shakir & Creswell, 2018). It is an 8-item questionnaire designed to assess symptoms of anxiety disorders in children. An initial evaluation of the questionnaire indicates it has good psychometric properties in children from age 7 to 11 (Reardon, et al., 2018). Only 1 of the 8 items are required to be collected to score this measure as 7/8 items overlap with those already collected within the RCADS-p. The additional item that enables us to calculate a SCAS-P-8 total score will be completed at baseline, and then at 14 and 26 weeks post randomisation by the parent/carer.

Derivation

Each of the 8 items is scored on a 4-point Likert scale ("0" never, "1" sometimes, "2" often, "3" always). The total score will be calculated as the sum of these 8 items, giving a possible range of 0 to 24. The items of the RCADS which make up this score are 1,9,18,27,32,34,43 and 48.

2.1.2.3 Overall Functioning (ORS)

Outcome Rating Scale (ORS). The ORS (Miller, Duncan, Brown, Sparks & Claud, 2003) will be used to assess functioning across different areas of the child's life. It comprises four simple rating scales in which the parent/carer rates how their child has been feeling over the last week (individually, interpersonally, socially, and overall wellbeing). Each item is rated using a variable length (as it is done online the length of the line is not always 10cm) visual analogue scale, with instructions to place a mark on each line. A higher score indicates better functioning. It has good reliability and validity (Bringhurst, Watson et al. 2006). The ORS will be completed at baseline, and then at 14 and 26 weeks post randomisation by the parent/carer.

Derivation

Each of the four visual analogue scales is approximately 10cm, but this varies due to it being done online. The proportion of the line along which the mark is made will be cacluated and converted to a 0-10 scale, measured to 1 decimal place. The four scores are added together to give an overall score. The total possible score is 40.

2.1.2.4 COMMON COMORBID EMOTIONAL AND BEHAVIOURAL PROBLEMS (SDQ-P)

Strengths and Difficulties Questionnaire (SDQ-P). The SDQ-P (Goodman, Meltzer & Bailey, 1998) is a behavioural screening questionnaire. It comprises of 5 scales assessing: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behaviour. It has satisfactory reliability (Yao et al., 2009; Goodman, 2001) and good concurrent and discriminant validity (Muris, Meesters & van den Berg, 2003; Lundh, Wangby-Lundh & Bjarehed, 2008). The parent-report version will be completed at baseline, and then at 14 and 26 weeks post randomisation.

Derivation

Each of the 25 questions is rated as “not true”, “somewhat true” or “certainly true”. These are scored as 0, 1 and 2 respectively, unless they are listed in the ‘items to be reverse scored’ column in the table below. For these items ‘not true’ will be scored as 2 and ‘certainly true’ will be scored as 0. For each of the 5 scales the score can range from 0 to 10 if all items have been completed. These scores can be scaled up pro-rata if at least 3 items have been completed.

The total difficulties score is generated by summing scores from all the scales except the prosocial scale. The resultant score ranges from 0 to 40, and is counted as missing if at least one of the 4 component scores is missing.

The separate scales in the table below will also be analysed separately.

Scale	Related Items	Items to be reverse scored
Emotional symptoms	3, 8, 13, 16, 24	None
Conduct problems	5, 7, 12, 18, 22	7
Hyperactivity/inattention	2, 10, 15, 21, 25	21, 25
Peer relationship problems	6, 11, 14, 19, 23	11, 14
Prosocial behaviour	1 , 4, 9, 17, 20	None

2.1.2.5 COVID-19 SPECIFIC WORRIES (PAS)

Pandemic Anxiety Scale (PAS). The PAS (McElroy et al., 2020) is a 9-item scale designed to capture specific aspects of the COVID-19 pandemic that are provoking anxiety, as well as to explore how these vary by health and demographic factors. An initial evaluation of the scale indicates that the PAS is a reliable and valid measure (McElroy et al., 2020) and based on parent and adolescent self-report comprised two factors (using 7 items): disease anxiety (e.g. catching, transmitting the virus) and consequence anxiety (e.g. impact on economic prospects). The PAS will be completed by the parent/carer at baseline, and then at 14 and 26 weeks post randomisation.

Derivation

The 7 item scale will be used for analysis. Each of the 7 questions is rated as "strongly disagree", "disagree" or "neither disagree/agree", "agree" or "strongly agree". These are scored as 0, 1, 2, 3 and 4 respectively.

The total score will be sum of questions 2, 3, 4, 5, 7, 8 and 9 (not including "My child thinks that COVID-19 is a very serious issue" or "My child is worried we won't have enough food and other essential items during the outbreak" . The total score will range from 0 to 28.

The 2 subscales will be calculated as the sum of the following:

- Disease anxiety – questions 2, 3, 4 and 5 (range 0-16)
- Consequence anxiety – questions 7, 8 and 9 (range 0-12)

2.1.2.6 HEALTH ECONOMIC MEASURES

Health economic outcomes will not be covered in this analysis plan.

2.1.2.7 TREATMENT CREDIBILITY AND EXPERIENCE (CEI)

Credibility and Expectation of Improvement Scale (CEI). Parent/carer will be asked to complete the CEI to assess participant expectations and views regarding treatment credibility, after randomisation and prior to treatment commencing (Borkovec & Nau, 1972). It consists of three items, rated on a scale from 0 "not at all" to 10 "completely", asking about how logical the treatment seems, confidence in its success at reducing their symptoms, and their likelihood to recommend the therapy to a friend with similar symptoms. This measure is administered after randomisation with reference to the treatment arm allocated.

An adapted version of the CEI will also be administered post treatment (14 weeks post randomisation), to give a retrospective account of treatment credibility (i.e. the questions are reworded to be considered in light of having received treatment).

We have also adapted the CEI to evaluate therapists' experiences of treatment within this trial. This comprises items referring to how logical they found the treatment, how comfortable they felt delivering the treatment, how prepared they felt, certainty in the success of the intervention, confidence recommending the treatment to other therapists, and likelihood of administering the treatment again.

Derivation

Each item will be analysed separately and will be a score ranging from 0 to 10.

2.1.2.8 ADVERSE EVENTS REPORTING OPPORTUNITY

CAMHS therapists will be asked to report any adverse events that they become aware of while working with families in either arm over the whole treatment period. We will also provide parents/carers and children an opportunity to describe any negative impacts of participating in the study after completing the questionnaires at 14 and 26 weeks and (for parents) after completing the qualitative interview. So as not to 'lead' answers we will enquire about positive and negative consequences of taking part in the treatment. The research team will regularly review responses to identify any responses that indicate the presence of an adverse event.

2.1.3 EXPLORATORY OUTCOMES

2.1.3.1 MEASURES ROUTINELY USED TO MONITOR OUTCOMES IN OSI

For the OSI+therapist support arm only, the OSI platform collects routine outcome measures and these will be used to help therapists to evaluate progress of participants through treatment and to explore the trajectory of participant improvement across the course of treatment. The OSI platform routinely collects the CAIS-P, RCADS-p, SCAS-P8, and ORS as described above, and session rating scales and goal-based outcomes as described below:

Session Rating Scales (SRS). The SRS (Duncan, Miller, & Sparks, 2003) assesses key dimensions of an effective therapeutic relationship and will be given at the end of each therapy session to get feedback from the parents/carers so that any issues related to therapeutic alliances can be immediately identified and addressed within treatment. The SRS comprises four simple rating scales in which the parent rates their experience of the treatment session (with regard to relationship with the therapist, goals and topics, approach or method and an overall rating). It uses the same visual analogue scale as the ORS. It has well-established reliability and validity (Duncan, Miller et al. 2003, Campbell and Hemsley 2009). The total score will be the sum of the 4 scales and will have a possible range of 0-40.

Goal Based Outcomes (GBOs). This is a simple rating scale in which the parent rates on an 11 point scale (0 – 10) the extent to which their child has made progress towards up to three treatment goals (Law & Jacob, 2015). Although this measure is now widely used in CAMHS (as part of the CYP IAPT initiative), its psychometric properties have not yet been established. This will be presented both separately for each treatment goal, and as a mean across all treatment goals.

Routinely collected sessional measures will be used to explore the trajectory of change within the OSI+therapist support arm only to inform future developments of the programme. We will not be collecting routine outcome measures from the treatment as usual arm for comparative purposes as these will vary according to site specific practice and treatment specific requirements.

2.1.3.2 QUALITATIVE INTERVIEWS WITH PARENTS/CARERS AND THERAPISTS.

Qualitive outcomes will not be covered in this analysis plan.

2.2 TARGET POPULATION

Children aged 5-12 with anxiety as the primary presenting problem, and their parents/carers.

Therapists who deliver psychological treatments within Child and Adolescent Mental Health Services in England.

2.2.1 INCLUSION CRITERIA

Child

1. is aged 5-12 years at intake
2. primary problem is anxiety
3. willing and able to assent

Parent/Carer

1. has sufficient English language to complete measures/ access interventions
2. family has access to the internet
3. is willing and able to provide consent.

Therapists

1. provides psychological treatment to children in participating services
2. willing and able to provide informed consent

2.2.2 EXCLUSION CRITERIA

Participants are not eligible if ANY of the following apply:

Child

1. has co-morbid conditions that are likely to interfere with treatment delivery, (established autism spectrum condition/ learning disability, suicidal intent/ recurrent or potentially life limiting self-harm)
2. is identified by social services due to child protection concerns.

Parent/Carer

1. has a significant intellectual impairment or severe mental health problem that is likely to interfere with treatment delivery.

2. is unable to access or understand the written English language materials necessary for the interventions.

Therapist

There are no exclusion criteria for Therapists.

2.3 SAMPLE SIZE

Between 418 and 560 children (209 - 280 per group) with an anxiety disorder and their parent/carer will be randomised across the two treatment arms. This sample size is considered to be sufficient to provide a standardised noninferiority margin=0.33 and between 80% - 90% power (allowing for 30% attrition).

2.4 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

Participants will be randomised in a 1:1 ratio to (i) OSI+therapist support or (ii) CAMHS Treatment as Usual for child anxiety problems within the COVID-19 context (C-TAU; typically 'face to face' treatment delivered over phone/video). Randomisation will be minimised by child age (<=8; >=9), gender, service type (school based or not school based), and baseline anxiety-associated interference. Participants will be randomised using a fully validated and secured web-based randomisation system called Sortition using blocked randomisation (with varying permuted block size) that will automatically occur after the participating parent/carer completes the consent and baseline measures, and the child completes assent (online). The treatment allocation will be communicated to the participants (child and parent/carer) in a follow-up email. The online system will also send an email to the clinical team providing information about treatment allocation for each participating family. Due to the nature of the trial, blinding is not possible to the trial participants of the allocated psychological therapy nor to the research team. The statistician conducting the analysis will be blinded to treatment allocation whilst analysing the primary and secondary outcomes. The exploratory analysis will be carried out after unblinding the statistician and either after version 1.0 of the Statistical Analysis Report is signed off or by a separate statistician. In order to minimise the risk of bias the statistical analysis plan will be finalised prior to analysis.

3 Analysis – General considerations

3.1 Descriptive statistics

Summary descriptions for continuous measurements will be means and standard deviations. Medians and interquartile ranges will be presented if more appropriate. Counts and percentages will be presented for categorical variables. Summary statistics will be provided by randomised group and overall.

3.2 Characteristics of participants

Baseline characteristics of the patients (demographics and baseline of all outcome variables where available) will be reported by randomised group as well as overall.

There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variables.

3.3 Definition of population for analysis

The primary analysis population is defined as all participants for whom data are available, analysed according to the groups they were randomly allocated to, regardless of treatment compliance. They must have completed their assessment within 4 weeks of the 14 week and 26 week time points.

Two sensitivity analyses will be carried out based on altering the time frame allowed for the assessments. These are detailed in section 6.

A per-protocol analysis will be carried out excluding those who have deviation from the protocol. Compliance with protocol to be included in the per protocol analysis will be defined as completing a minimum of the first 5 treatment sessions (sessions 0, 1, 2, 3 and 4) for participants in either arm.

3.4 Pooling of investigational sites

Service type (school vs clinic) is used as a minimisation variable in the randomisation model and so will be included in the primary analysis model. No other clustering by site is assumed.

3.5 Data Monitoring Committee And Interim Analyses

A Trial Steering Committee (TSC) will be convened and will meet approximately every 4 months throughout the study. Recruitment to the trial will be rapid and no interim analyses are planned so a separate Data Monitoring and Ethics Committee will not be formed, however we reserve the option to form one if the TSC deem it necessary at any point during the trial.

Due to the rapid nature of the trial there is not an internal pilot and there are no formal stopping criteria. There is no planned interim analysis.

4 PRIMARY ANALYSIS

4.1 PRIMARY OUTCOME

Analysis of the primary outcome will be performed using a generalised linear mixed effects model adjusting for minimisation variables, will be used to determine the difference in means between the 2 groups and it's 95% confidence interval. The mixed effect models will include the outcome as the response variable, time point, randomised group, and baseline score as fixed effects and a participant specific random intercept. An interaction between time and randomised group will be fitted as a fixed effect to allow estimation of treatment effect at all time points. Additionally the following minimisation variables will be included as fixed in the model: child age,gender, baseline anxiety associated interference and service type (school vs clinic). . The primary endpoint of interest is 26 weeks, although measures at 14 weeks will also be included in the model to assist with estimation in the presence of missing data. Non-inferiority is claimed if the lower limit of the 95% confidence interval around the standardized effect size is less than -0.33. A P-value for the null hypothesis of inferiority of the OSI intervention compared to usual care will also be calculated.

4.2 HANDLING MISSING DATA

The availability of the outcome data for the primary outcome will be summarised by randomised group. Missing primary outcome data will be reported overall and by randomised group. The primary analysis model is valid under a missing at random (MAR) assumption, that is, it is valid if variables predictive of missingness are included in the model.

Additionally baseline characteristics will be summarised by availability of the primary outcome and logistic regression models will explore any association between baseline characteristics and availability of the primary outcome. Covariates found to be predictive of missingness ($P< 0.05$) will be included in the analysis model in a sensitivity analysis of the primary outcome.

4.3 HANDLING OUTLIERS

Any outliers will be checked and verified to ensure that they are true values. Outliers will be identified as those observations more than four standard deviations from the mean. Once they have been confirmed, a sensitivity analysis will be carried out to assess the impact of these values on the results by excluding these participants.

4.4 HANDLING MULTI-CENTRE/CLUSTERED DATA

Randomisation was minimised byservice type (school vs clinic) and this will be included in all models. No other clustering by site is assumed.

4.5 Multiple comparisons and multiplicity

A single primary outcome is specified in the protocol and the secondary outcomes are considered exploratory, so no adjustment for multiple comparisons will be carried out.

4.6 Model assumptions

The primary analysis model assumes normality of the residuals. The distribution of the primary outcome will be assessed and the assumptions of the model will be checked. If any of the assumptions are violated, then p-values and confidence intervals for the model coefficients will be obtained by means of bootstrapping.

5 SECONDARY ANALYSIS

5.1 Secondary outcomes

Secondary outcomes will be analysed in the same way as the primary outcome using a generalised linear mixed effects model adjusting for minimisation variables.

5.2 Exploratory outcomes

5.2.1 Treatment credibility

Treatment credibility, acceptability and experience scores will be calculated and compared for both treatment groups, using simple mean comparisons. Comparisons of means will be carried out using a t-test or suitable non-parametric equivalent (Mann-Whitney-U) if the distributions are non-normal.

5.2.2 Trajectory Of Change Reported Within The Osi Arm

Measures collected only in the OSI arm will be summarised at each time point. Change in child symptoms and functioning on a sessional basis will be plotted to explore the trajectory of change in the OSI arm.

6 SENSITIVITY ANALYSIS

If outliers are identified, a sensitivity analysis excluding these outliers will be carried out to determine the impact of these observations on the treatment effect of the primary outcome.

As a sensitivity analysis of the primary outcome, baseline covariates found to be predictive of missingness will be included as main effects in the linear mixed effects model.

The primary analysis will be repeated in the per-protocol population excluding those who have deviation from the protocol. Compliance with protocol to be included in the per protocol analysis will be defined as completing a minimum of the first 5 treatment sessions for participants in either arm (modules 0-4).

Two sensitivity analyses of the primary outcome will be carried out based on altering the window in which the assessments must have been made. They are as follows:

1. Include all outcomes, regardless of the length of time elapsed from either 14 or 26 weeks.
2. As above, but if the 26 week outcome is missing and the 14 week outcome has been collected within ±4 weeks of 26 weeks, treat this as the 26 week outcome.

7 SUBGROUP ANALYSES

There is no planned subgroup analysis.

8 SAFETY ANALYSIS

Adverse events (AEs) and serious adverse events (SAEs) will be summarised according to severity and relatedness by treatment arm.

A Serious Adverse Events (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

There is a very low risk of SAEs in the current trial, however the following details a non-exhaustive list of potential SAEs and Adverse Events (AE):

Potential Serious Adverse Events (SAEs) (to parent/child):

1. Admission to psychiatric hospital (parent/child);
2. Sectioned under the Mental Health Act;
3. Significant and sustained deterioration of pre-existing mental health condition that requires immediate intervention that cannot be accommodated within the treatment protocol (as determined in clinical supervision);
4. Diagnosis of new mental health condition;

5. Suicidal behaviour;
6. A serious safeguarding issue is revealed.

Potential Serious Adverse Events (SAEs) not directly related to the trial and Adverse Events (AEs):

1. Children's schooling or parent/guardians work is adversely affected (e.g. due to time spent in therapy or assessments encroaching on school or homework time).
2. One or more aspect of the therapy or assessment procedure induces unacceptable levels of distress for either the participant, their parent/guardian, or the therapist.
3. It becomes apparent that one of more of the exclusion criteria is met (or inclusion criteria not met) by the participant. [NB. This will be logged but the participant remains in treatment as long as clinically appropriate and retained in the intent to treat sample].
4. A sustained and significant increase in detrimental behaviours (e.g. safety seeking behaviours) as determined by any of the outcome measures collected throughout the study.
5. The emergence of new detrimental behaviours (e.g. self-harm).
6. Drop-out of treatment / request to change therapist.
7. Any actual or potential breach of confidentiality.
8. A complaint is received from a participant, their parent/guardian, or the therapist referring to an actual or perceived adverse event as defined above.

The window for reporting SAEs and AEs will be:

(i) During the treatment phase based on therapist report

(ii) Up to the end of study based on parent/carer report (i.e. up to the 26 week assessment or qualitative interview, whichever is later).

The 14 week and 26 week assessments within this trial will include questionnaires monitoring participants' functioning and quality of life, therefore, some of the potential adverse events identified in this document will be monitored routinely. Therapists will also be asked to indicate the presence of an SAE or AE that arises during the course of treatment.

9 VALIDATION

A second Trial Statistician will validate the primary outcome and safety data analyses and review the statistical analysis report.

10 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

None to report.

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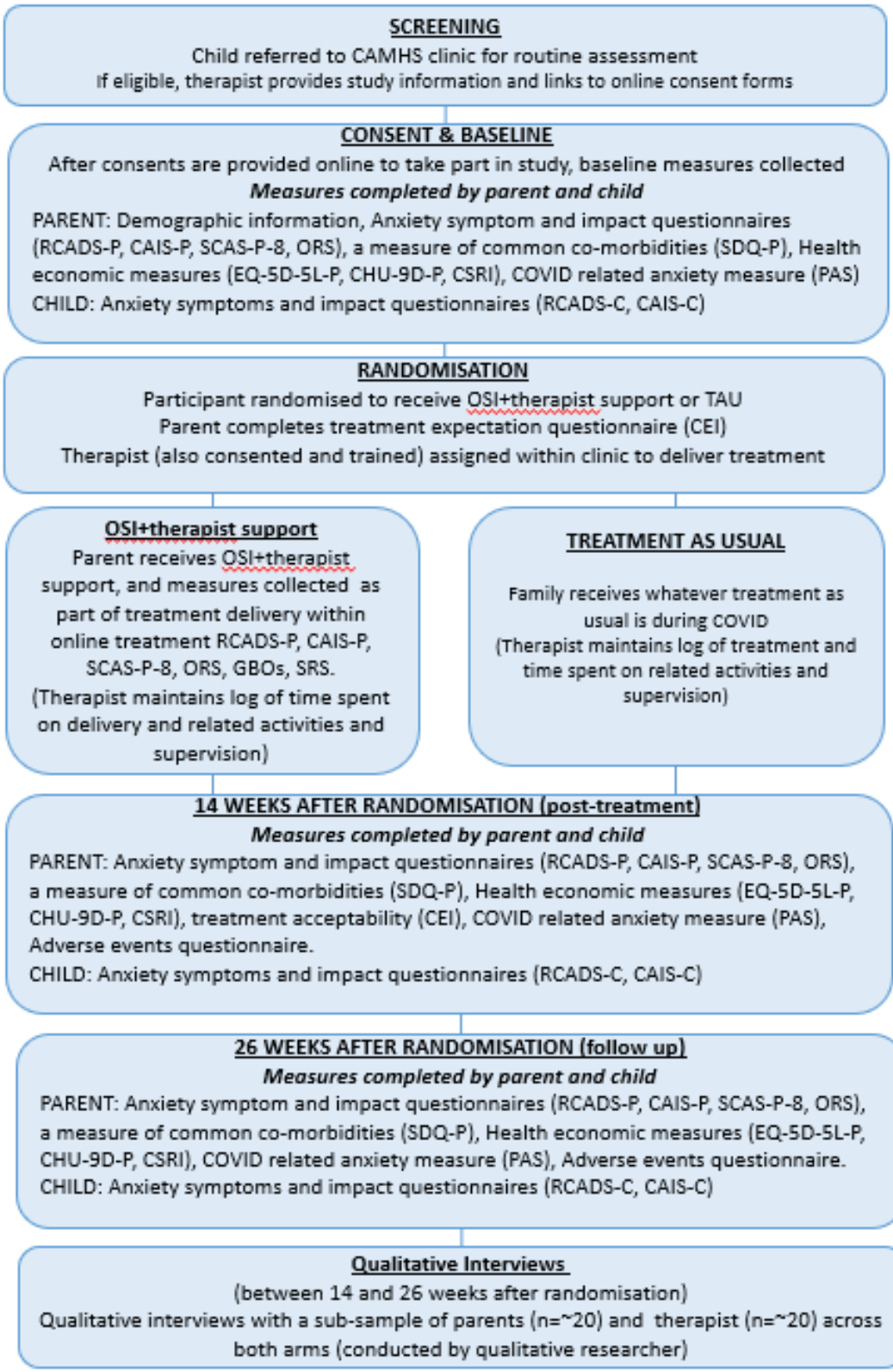
12 APPENDICES

12.1 APPENDIX A: FLOWCHART OF TRIAL PROCEDURES



12.2 APPENDIX B: FLOW DIAGRAM OF TRIAL PARTICIPANTS