Study Title:
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

Internal Reference Number / Short title:
Child Anxiety Treatment in the context of COVID-19 (Co-CAT)

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Funder:	• National Institute for Health and Social Care Research (NIHR)

- Department of Health and Social Care (DHSC)/UK Research and Innovation (UKRI) COVID-19 Rapid Response Initiative (managed by the Medical Research Council)

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The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Please declare any/no potential conflicts of interest.

The Online Support and Intervention (OSI) intervention is based on underpinning evaluations of a book-based treatment approach for child anxiety disorders. No investigators receive any financial reward for the use of OSI, however the CI receives royalties for the sale of a parent book and a therapist book that some of the underpinning work is based on.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Amendment History

Number	Protocol Version	Version Date	Author	Details of Change
n/a	1.0	26.08.2020	(Whole Team)	Original
1	1.1	08.10.2020	L Taylor	Correction of randomisation details to using minimisation not stratification Other minor edits to correct inconsistencies
2	2.0		L Taylor	Edits to improve consistency throughout and to fully reflect final study procedures and processes In particular: • Change from England to UK to reflect broadening of study sites • Additional Exclusion Criteria • Addition of new Study & Schools Flyer • Removal of "Any actual or potential breach of confidentiality" from the Adverse Event list
3	2.1	16.07.2021	L Taylor	In Section 3, SYNOPSIS: Planned Study Period, updated from 12 months to 22 months following extension from funder Planned Recruitment period, updated from months 2-4 month to months 4-15 following extension from funder
4	2.2	08.11.2021	L Taylor & E Brooks	In Section 3, SYNOPSIS: Planned Study Period, updated from 22 to 31 months following extension from funder. Planned Recruitment Period, updated from Months 4-15 to Months 4-24

				Minor edits to frequency of TSC meetings and referring to OSI sessions as modules rather than weekly
5	2.3	15.07.2022	L Taylor & E Brooks	In Section 3, SYNOPSIS and Section 11.3 Sample Size Determination updated to reflect sample size requirements from just 90% power to both 80% and 90% power.
6	2.4	02.09.2022	M Violato & L Taylor	Minor edits to Health Economic Sections Section 4 – Abbreviations - correction to abbreviations Section 6 – Objective and Outcome Measures - (2) clarification that school attendance is parent report Section 9.7.7 Health Economic Measures - update of references Section 11.10 Health Economic Analysis - addition of reference to the Health Economic analysis plan (HEAP) - update of references - Clarification that the cost effectiveness analysis (CEA) will include the CAIS-P (the primary outcome)
7	2.5	21.10.2022	L Taylor & E Brooks	Addition of new funder for project extension as original COVID Funding Stream closed.

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1. KEY CONTACTS

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2. LAY SUMMARY

In the context of COVID-19, NHS Child and Adolescent Mental Health Services (CAMHS) and other children's mental health services face major challenges in providing psychological treatments that (i) work when delivered remotely, and (ii) can be delivered efficiently to manage an anticipated increase in referrals as social distancing measures are relaxed.[1]

[1] For the purposes of this document and other study documentation, when we refer to CAMHS we include Local Authority and Third Sector organisations that provide child mental health care on behalf of the NHS.

Anxiety problems are a common reason for referral to CAMHS, children with pre-existing anxiety problems are particularly vulnerable in the context of COVID-19, and there are concerns about likely increases in childhood anxiety as schools reopen.

We worked with children, parents, and NHS clinicians to develop a brief online parent-led cognitive behavioural treatment (CBT) delivered by the OSI platform that parents/carers of children with anxiety disorders work through with remote support from a CAMHS therapist. We will now test whether access to the OSI platform together with therapist support works as well as what CAMHS are otherwise offering to help children with anxiety problems (whatever this might be while social distancing measures are in place and in the post COVID-19 recovery phase), and whether OSI as delivered with therapist support brings economic benefits. We will also provide an understanding of parents' and therapists' experiences of digital treatments in children's mental health services in the context of COVID-19.

This research has the potential to create a step change in the digital delivery of treatments in CAMHS and other children's mental health services, bringing benefits in the COVID-19 context and beyond.

3. SYNOPSIS

Study Title	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
Internal ref. no. / short title	Child Anxiety Treatment in the context of COVID-19 (Co-CAT):
Study registration	ISRCTN12890382 (registered 23/10/2020) https://doi.org/10.1186/ISRCTN12890382
Sponsor	University of Oxford Clinical Trials and Research Governance Joint Research Office 1st floor, Boundary Brook House

	Churchill Drive, Headington, Oxford OX3 7GB		
Funder	National Institute for Health and Social Care Research (NIHR) DHSC/UKRI COVID-19 Rapid Response Initiative		
Study Design	Multi-site, two arm, parallel group, randomised non-inferiority trial		
Study Participants	1. Children aged 5-12 years referred to Child and Adolescent Mental Health Services in England for treatment for anxiety problems 2. Parents of children aged 5-12 years referred to Child and Adolescent Mental Health Services in England for treatment for anxiety problems 3. Therapists who deliver psychological treatments within Child and Adolescent Mental Health Services in UK		
Sample Size	N = Between 418 and 560 (209-280 per arm) parent-child dyads N= approx. 40 therapists		
Planned Study Period	Total length – 31 months		
Planned Recruitment period	Months 4 - 24		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To evaluate the parent-reported clinical effectiveness of a brief parent-led cognitive behavioural treatment (CBT) delivered by the OSI platform with therapist support (OSI+therapist support) for the treatment of child	The Child Anxiety Impact Scale- parent report (CAIS-P)	26 weeks post-randomisation

	anxiety compared to 'COVID-19 treatment as usual' (C-TAU) in CAMHS		
Secondary	To further evaluate the clinical effectiveness of OSI+therapist support for the treatment of child anxiety compared to 'COVID-19 treatment as usual' (C-TAU) in CAMHS	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
	To 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). Client Service Receipt Inventory including 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	To explore the trajectory of change	Measures used to monitor child outcomes built in to	Weeks 1-7 of treatment

	reported within the OSI arm	OSI (RCADS-P, CAIS-P, SCAS-8P; ORS; SRS; GBOs),	(Modules 0-6)
	To understand therapist and parents' experiences of treating child anxiety in the COVID-19 context (across both arms)	Qualitative interviews Therapist experience of treatment questionnaire	14 -26 weeks post-randomisation End of each treatment delivered
Intervention(s)	Online psychological intervention for child anxiety with therapist support (OSI+therapist support). OSI is an online platform for sharing content and record keeping as part of a brief therapist-supported parent-led cognitive behavioural treatment (CBT) .		
Comparator	Treatment as Usual for children with anxiety in clinical Child and Adolescent Mental Health Services in the COVID-19 context (C-TAU)		

4. ABBREVIATIONS

AE	Adverse Event
AES-256	Advanced Encryption Standard - 256
AHSN	Academic Health Science Networks
AnDY	Anxiety and Depression in Young People Research Clinic (University of Reading)
CAIS-C	Child Anxiety Impact Scale - Child
CAIS-P	Child Anxiety Impact Scale - Parent
CAMHS	Child and Adolescent Mental Health Services
CBT	Cognitive Behavioural Therapy
CEA	Cost Effectiveness Analysis
CEI	Credibility and Expectation of Improvement Scale

CHU-9D	Child Health Utility - 9-Dimension
CI	Chief Investigator
Co-CAT	Child Anxiety Treatment in the context of COVID-19
Co-SPACE	COVID-19: Supporting Parents, Adolescents and Children during Epidemics
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CSRI	Client Services Receipt Inventory
C-TAU	Treatment as Usual in the context of COVID-19
CTRG	Clinical Trials & Research Governance, University of Oxford
CUA	Cost Utility Analysis
CYP	Children and Young People
DHSC	Department of Health and Social Care
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol -5 Dimension 5 - Level (adult quality of life instrument)
ePRO	Electronic Patient Reported Outcome
GBO	Goal Based Outcomes – Goal Progress Chart
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
HTTPS	Hypertext Transfer Protocol Secure
IAPT	Improving Access to Psychological Therapies
ICER	Incremental Cost-Effectiveness Ratios
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors guidelines
IRAS	Integrated Research Application System
IP	Internet Protocol
ISF	Investigator Site File

ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
MRC	Medical Research Council
MSD	Medical Science Division
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
OID	Organisational Information Document
OSI	Online Support and Intervention (for child anxiety)
PC-CTU	Primary Care Clinical Trials Unit
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
Q&A	Question and Answer
QALY	Quality-adjusted Life Year
RCADS-C/P	Revised Children's Anxiety and Depression Scale – Child/ Parent
RCT	Randomised Controlled Trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RES	Research Ethics Service
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCAS-P8	Brief Spence Children's Anxiety Scale-Parent Version
SDQ-p	Strengths and Difficulties Questionnaire- parent report
SOE	Schedule of Events
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SRS	Session Rating Scale
SSL	Secure Socket Layer Encryption
TAU	Treatment as Usual

TMG	Trial Management Group
TSC	Trial Steering Committee
UKRI	UK Research and Innovation
VAS	Visual Analogue Scale

5. BACKGROUND AND RATIONALE

Background

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). As a result, societal costs for anxiety disorders are substantial, with estimated total costs in England of £8.9 billion, expected to rise to £14.2 billion by 2026 (McCrone, Dhanasiri, Patel, Knapp, & Lawton-Smith, 2008).

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). A recent UK survey found that more than 60% of children with anxiety disorders had not received any professional support, and only 2% had received CBT (Reardon, Harvey, & Creswell, 2018). Families face extensive barriers accessing professional support for child anxiety disorders, including high demands on services, limited available support, and long waiting lists (O'Brien, Harvey, Young, Reardon, & Creswell, 2017; Reardon, Harvey, Young, O'Brien, & Creswell, 2018).

Traditional CBT for child anxiety disorders is typically lengthy and involves specialists working directly with the child. We have developed a briefer version of the traditional treatment that involves working directly with parents, and supporting them in helping their child overcome their difficulties with anxiety. This brief parent-guided treatment has similar outcomes to the traditional approach, and can be delivered by non-specialists (Creswell et al., 2017; Thirlwall et

al., 2013). However, 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. In a recent survey of parents of children with elevated anxiety, all parents had some form of internet access, and more than 85% of parents reported that online treatment delivery would reduce stigma for families and allow families to use it at any time, and from home (Reardon, Hill, O'Brien, & Creswell, 2018).

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 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, including fears about leaving the house, and a significant increase in emotional symptoms in primary school aged children during lockdown (Co-Space Report 3, 2020). CAMHS and parents are concerned child anxiety will increase as we approach the post-lockdown phase and schools reopen (Health Innovation Network South London, 2020).

In our Co-SPACE study, parents reported that they wanted help via online materials and personalised support from a professional, however there are currently no evidence-based platforms available to CAMHS to do this (Pennant et al., 2015). From extensive contact with CAMHS therapists, we understand that they are typically delivering 'face to face' therapy via phone/videocall, but have little evidence about how to do this most effectively and efficiently. 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. The OSI platform has recently been introduced into the Anxiety and Depression in Young People (AnDY) Research Clinic at the University of Reading following a codesign and usability testing phase with good engagement from families. However, 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 (administering face to face treatments, adapted by individual therapists/teams for delivery via telephone/video call) 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 and other children's mental health services 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 therapist 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.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To evaluate the parent-reported clinical effectiveness of a brief parent-led cognitive behavioural treatment (CBT) delivered by the OSI platform with therapist support (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 (parent reported 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 (Modules 0-6)
(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

7. STUDY 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 and other child mental health services '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). See Appendices 1 and 2.

8. PARTICIPANT IDENTIFICATION

8.1 Study Participants

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

Therapists who deliver psychological treatments within children's mental health services in the UK.

8.2 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

8.3 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,
3. is identified via a Schools Team and is in Reception year,year 1 or year 2 in a school that is taking part in the MyCATS (ISRCTN Registration Number: 82398107) study (another study where the child may receive the OSI intervention).

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.

9. PROTOCOL PROCEDURES

A flowchart summarising the trial procedures can be found in Appendix 1.

9.1. Recruitment

Identifying Trial Sites

We will invite NHS Child and Adolescent Mental Health Services, CAMHS (and Local Authority and Third Sector organisations that provide child mental health care on behalf of the NHS) to be trial sites in the study. We will invite teams to join the study through the following routes (i) direct contact to teams that have expressed an interest in the study/OSI or have participated in previous randomised controlled trials, (ii) contact through the NHS Future Collaboration Platform (Parent Led CBT workspace), (iii) contact through local and regional networks and collaborations (AHSN, children and young people's IAPT training centres), (iv) clinical research network support teams. Teams will be provided with a Study Flyer to give a

brief overview of the study. Where services include School Mental Health Support Teams, there is an additional Schools Flyer that can be provided to schools where the Teams take referrals from to help schools identify eligible participants.

Additionally, therapists at each participating site may be invited to participate in a qualitative interview after delivering treatment.

Recruitment of participants by clinical teams
Participating families will be identified by their clinical teams. All eligible therapists within the participating teams will be invited to participate, with their managers' approval. Clinical teams will follow their usual procedures to identify the child's primary presenting problem. Where the clinical team identify that the study inclusion criteria are met (and exclusion criteria are not) they will briefly outline the study to the parents/carers. If parents/carers express an interest in the study, they will be asked to provide an email address to which they will be sent a secured link to the study IT system where the parent/carer will be able to access online information sheets which will provide further information about the study and what would be expected of the participants alongside contact details for the study team (email and phone number) so that they can be contacted to answer any questions. There will also be video information (information sheet text being read aloud verbatim). In addition, there are dedicated, age appropriate, online information and video (consisting of the information sheet with text being read aloud verbatim) for the child.

There is the opportunity for parents to provide consent and their contact details. Where parents provide consent, a further email will be sent with a link for the child to provide assent.

Therapists whose role includes delivery of psychological interventions to children with anxiety problems within participating clinical teams will be invited to take part and consenting families will be allocated to these therapists for treatment.

9.2. Screening and Eligibility Assessment

The clinical team will conduct an initial assessment of eligibility according to the inclusion and exclusion criteria.
If the child is eligible for inclusion and the parent/carer is happy to continue, the clinical team will confirm eligibility and provide the parent a secured link to access the information sheets

online (in written and video form) prior to being invited to provide online consent for themselves and their child (followed by child providing online assent).
The clinical team will be informed when a parent consents and child assents to the study and they are randomised. The research team also monitor participant progress and inform clinical teams where families do not consent to take part. Clinical teams are asked to contact parents if no randomisation email is received after one week of approach. This is so that the clinical team can organise alternative care if necessary.

9.3. Informed Consent

Parents/carers will provide online consent for themselves and their child. Children will provide online assent.

Participant Information (parent/child/therapist) will be provided in written and video form (for parents and children) detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. Each potential participant will be given sufficient time to read through the participant information sheet and ask questions, either to the clinical contact or the research team, before deciding whether to take part.

If clinical teams have not been notified that a participating family has consented/assented to the study within two weeks of approach, they will be free to contact the participant to arrange alternative treatment. Clinical teams will be notified two weeks before the recruitment window is coming to an end so that they can inform any families that have not yet responded how much time they have left to consent/assent should they wish to participate.

Participants must provide their name and date the latest approved version of the Informed Consent form (via a unique link) before any study specific procedures are performed. A copy of the signed informed consent/assent forms will be available to be downloaded at each timepoint when the parent/carer accesses the system and notice of this will also be emailed to the local investigator (or their delegated authority) who will also have access to download these from the system for adding to the child's medical record.

Therapists invited to take part in a qualitative interview will be provided with a study information sheet by email and/or via the study website. A privacy notice will also be supplied. Consent will be obtained from the therapist at the time of interview, prior to recording. The researcher will read the consent clauses and record responses. They will email a copy of the consent form securely to the participating therapist.

9.4. Randomisation

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.

9.5. Blinding and code-breaking

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.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

9.6.1. Description of study intervention(s)

OSI (Online Support and Intervention for child anxiety) is an online adaptation of an evidence-based brief parent-guided CBT program for the treatment of anxiety problems in preadolescent children. OSI comprises a parent website, accompanying therapist case management system, and

accompanying child game app (see attachment). The 7 modules are supported by weekly* 20 minute telephone/video call sessions between the parent/carer and a therapist and a review session 4 weeks after the final treatment session. (*or adjusted by family/clinicians if required) Therapists will receive a video-based training programme (45 minutes) and a treatment manual. All teams will be offered regular Q&A sessions throughout the treatment delivery phase to support set-up and delivery. Clinical supervision will be provided within teams following their usual procedures.

9.6.2. Description of comparator(s)

'COVID-19 Treatment as Usual', i.e. whatever treatment the participating services are delivering to treat child anxiety problems in the COVID-19 context.

9.6.3. Description of study procedure(s)

Where parent/carer and their child provide online consent or assent, respectively, they will be asked to complete online baseline assessments (all questionnaires), prior to randomisation. After randomisation, parents will be asked to complete a further short questionnaire about treatment expectations and acceptability.

Treatment in both arms will be organised by the clinical teams and will start as soon as possible and at most within 12 weeks of randomisation.

Families allocated to the intervention arm will access OSI and a member of the clinical team will provide support as they work through each OSI module. OSI incorporates routine outcome measures that are used for clinical purposes, but are also available to the research team through the OSI researcher portal in pseudo-anonymised form. Usage data are also available through the OSI researcher portal that provide detailed information on parents use of the website: frequency of sessions on the website, time spent on the website and also time spent on the different activities. This information will be used to describe compliance with the intervention.

Participating parents/carers and children in both arms (OSI+therapist support and C-TAU) will be sent a link to complete post-treatment and follow-up assessments (questionnaires) online 14 and 26 weeks after randomisation.

Therapists will provide information on 'COVID-19 Treatment as Usual' within the therapist logs in order for us to be able to describe what CAMHS and other children's mental health services are delivering in the COVID-19 context, specifically the treatment approach being followed, who they are having contact with (e.g. child, parent/carer, both) and for how long.

Therapists will provide brief demographic information at the study outset, will record information on activity with each participating family, and will complete a brief questionnaire about their experience of the treatment after completing treatment with each participating family.

We will also conduct qualitative interviews with a subgroup of parents and therapists (n= 25-40), purposively sampled on the basis of demographics and we will continue to sample to ensure variability in treatment outcomes across both arms if possible, to explore and to understand therapist and parent/carers' experiences of treating child anxiety in the current context.

9.7. Assessments

Assessments will be completed via online self-report questionnaires, administered at baseline, 14 weeks post-randomisation (post-treatment) and 26 weeks post-randomisation (follow-up). The research team will keep careful track of assessment completion and will contact participants (by email, text, phone) if measures have not been completed within 3 days of the invitation to complete measures (at all timepoints).

A summary of the measures that are provided at each timepoint is given in Appendix 2. All measures will be collected at all three time points with the following exceptions:

- Demographic information is only collected at baseline
- Treatment credibility will be collected post randomisation, prior to treatment starting and also at post-treatment to capture any differences in parent/carer treatment expectations between the two treatment arms.
- A brief question seeking information about potential adverse events/experiences will be asked at post-treatment and follow-up.
- Therapists will be asked to complete a treatment experience questionnaire at the end of treatment with each participating family. This is part of their delivery of the intervention.

9.7.1. Demographic information

Participating child and parent/carer demographics will be collected based on parent/carer report. The data collected will include (i) parent/carer age and child date of birth, (ii) parent/carer and child gender, (iii) parent and child ethnicity, (iv) child use of medication, (v) parental education, (vi) parental employment status and occupation, (vii) household circumstances, (viii) employment and income details and (ix) child's school type and education provision. This information will be used to describe the sample, inform randomisation minimisation, and to inform the health economic evaluation.

In order to describe therapists who delivered the treatment in this study, therapists will provide information on (i) their age, (ii) gender, (iii) ethnicity, (iv) professional background, (v) years qualified and of clinical experience, (vi) current working arrangements, (vii) experience of working with children with anxiety problems, (viii) relevant training, (ix) preferred ways of working with children with anxiety problems and their families.

9.7.2. Impact of Child Anxiety

The Child Anxiety Impact Scale- parent report (CAIS-P/C). The CAIS-p/c 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. An additional 4 'global' items assess overall interference. 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 CAIS-c/p will be completed at baseline, and then at 14 and 26 weeks post randomisation by both parent/carer and child.

9.7.3. Symptoms of Child Anxiety

Revised Child Anxiety and Depression Scale-Child and Parent version (RCADS-c/p). The RCADS-c/p is 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 has 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.

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 will be completed at baseline, and then at 14 and 26 weeks post randomisation by the parent/carer, and is added as an additional item at the end of the RCADS-P questionnaire.

9.7.4. Overall Functioning

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 10-centimetre 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.

9.7.5. Common comorbid emotional and behavioural problems

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.

9.7.6. COVID-19 specific worries

Pandemic Anxiety Scale (PAS). The PAS (McElroy et al., 2020) is a 7-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. It comprises two factors: disease anxiety (e.g. catching, transmitting the virus) and consequence anxiety (e.g. impact on economic prospects). An initial evaluation of the scale indicates that the PAS is a reliable and valid measure for use with parents (McElroy et al., 2020). The PAS will be completed by the parent/carer at baseline, and then at 14 and 26 weeks post randomisation.

9.7.7. Health economic measures

EQ-5D (5L) (parent self-report). The EQ-5D (5L) will be used to assess parent/carer's quality of life (Herdman et al, 2011). It is a well-validated measure of health-related quality of life, designed to estimate quality adjusted life years (QALYs), that is widely used across disease areas. It contains five questions, each related to a different domain of everyday life (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). For each domain the respondent has to indicate whether they experience no problems, slight problems, moderate problems, severe problems, or extreme problems. It also includes a visual analogue scale (VAS) for participants to rate their overall health on a scale from 0 ("worst imaginable health") to 100 ("best imaginable health"). The respondent's answers provide a description or profile of the respondent's quality of life, and a weight or value can then be placed on each profile using an existing UK tariff derived from the general public (Dolan, Gudex, Kind & Williams, 1995; NICE, 2022; Hernanes, Pudney & Wailoo, 2020; Hernandez, Wailoo & Pudney, 2017). The Eq-5D-5L will be completed at baseline, and then at 14 and 26 weeks post randomisation by the parent/carer.

CHU-9D-proxy version (parent report on child). The CHU-9D is a paediatric measure of health-related quality of life, which allows the calculation of QALYs for use in cost utility analysis. It includes nine dimensions (worried, sad, pain, tired, annoyed, schoolwork, sleep, daily routine, activities) each with five levels, and has been validated in child and adolescent populations (Stevens, 2011). Parent/carers will complete the proxy version at baseline, and then at 14 and 26 weeks post randomisation.

Client Services Receipt Inventory (CSRI) – children's version (parent report). A modified version of the CSRI (Beecham, 1999) will be used to collect information on patient-level resource use for both children (parent/carer-report on children) and parent/carer (self-report). Parent/carers will

be asked to report use of health, social care and non-NHS services, medications and parental time off work, school, and leisure activities at baseline (based on the prior 3 months), and then at 14 and 26 weeks post randomisation. Parent/carers will be provided with health diaries to facilitate recall of parent/carer and child's resource use.

Therapist Economic Logs (Supervision Logs and Treatment Logs). We will collect "Economic Logs from Therapists" during the treatment phase (up to 26 weeks if applicable, for example in the C-TAU arm where there is no set end point to the treatment). Therapists in both trial arms will be asked to complete an economic log throughout treatment, to record all staff-time spent on treatment-related activities (e.g. training and supervision, preparation of sessions, administration, phone contact with parent/carer, video-contact with child whenever applicable). Completion of these logs is part of their delivery of the research study.

9.7.8. Treatment Credibility and Experience

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. Completion of this is part of their delivery of the research study.

9.7.9. Adverse events reporting opportunity

Trial 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.

9.7.10. 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).

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 have 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.

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.

9.7.11. Qualitative interviews with parents/carers and therapists.

We will conduct qualitative interviews with 25-40 parents/carers and therapists, purposively sampled on the basis of demographics and treatment outcomes to explore therapist and parents' experiences of treating child anxiety in the current context. We have previously found that this sample size is sufficient for data saturation. Qualitative interviews will be conducted between post-treatment and follow up (between 14 and 26 weeks after randomisation). Interviews will be conducted by a qualitative researcher. Interviews will be topic-guided and the topic-guide will be developed and finalised following consultation with PPI representatives (indicative topic-guide provided in project documents).

We will invite 10 parents and therapists from the first 20 to complete treatment to take part in the qualitative interviews, and will review their demographics and treatment outcomes to identify characteristics that have not been represented using a grid developed specifically for this study to identify future participants to invite to take part (i.e. following a purposive sampling approach to ensure diversity among participants). We will initially invite participants to take part in the interview by email, and will follow this up with telephone/text message (up to three times). Interviews will be conducted remotely via Microsoft Teams (Teams) or over the telephone. Interviews will be audio recorded through an encrypted digital recorder. Recordings will be uploaded within 24 hours to the restricted access study z drive folder. Recordings will be transcribed by the research team (manually or using Teams), or by a third party provider who is a University registered supplier and will be required to adhere to recommendations from an Oxford University Third Party Security Assessment (TPSA). The transcriber will be required to delete all audio files after returning the verbatim transcription to the research team. Information that could reveal the identity of a participant to other people will not be included in transcriptions. Transcripts will then be uploaded to NVivo (Bazeley and Jackson 2019) for analysis and the NVivo Hermeneutic Unit saved in a secure OneDrive folder

9.8. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with the study procedures

- Participant decision

In the case of participant withdrawal, we will retain data collected only until that point unless the participant requests otherwise or agrees to take part in the further assessments.

It is also possible that the clinical team might withdraw the participant from the research treatment (OSI+therapist support) if allocated. If the therapist delivering treatment feels the child should not continue with OSI+therapist support (e.g. due to serious comorbidities arising that need to be addressed), we will retain data and continue to invite the participant to take part in further assessments, unless the participant requests otherwise.
The number of withdrawals from treatment and/or follow-up measures will be logged with a summary of their reasons (if offered by the participant).

9.9. Definition of End of Study

The end of study is the last patient assessment or qualitative interview.

10. SAFETY REPORTING

10.1. Definition of Serious Adverse Events

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 (all routinely monitored for presence of AEs).
7. 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. Further investigation will be made by the clinical team and the PI and the SAE/AE procedures will be followed where applicable. Specifically, the clinical team and the PI will assess the frequency and severity of the adverse event(s) and determine whether the participant should be withdrawn from the trial. The decision of the clinical team will be taken in the event that consensus isn't reached. Participants will also be given the opportunity to report adverse events anonymously after the parent/carer and child complete questionnaires at 14 and 26 weeks and in person (remotely) after the qualitative interviews (for the parent/carers). The research team will regularly review responses to identify any responses that indicate the presence of an adverse event and will report summaries of these responses to the Trial Steering Committee for review.

10.2. Reporting Procedures for Adverse Events/ Serious Adverse Events

All AEs and SAEs (both those relating to the trial and not directly relating to the trial) will be recorded, logged and monitored by the PI and TMG. If an AE is reported more than once for a participant, or more than three times during the study, it will be treated as an SAE.

A serious adverse event (SAE) occurring to a participant will be reported to the REC that gave the favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form.

In the event that a complaint is received from a participating parent/carer or child, the therapists, their managers, and the CI will attempt to resolve the issue as far as is possible. In the event that a

complaint is received from a participating therapist, their managers and the CI will attempt to resolve the issue as far as is possible. If this is not possible, and the issue remains unacceptable to participants, formal complaints will be logged and dealt with by the sponsor's representative in liaison with the CI. Those indicating an AE or SAE will be logged accordingly.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here. Details will be fully described in a statistical analysis plan (SAP). The SAP will be prepared by an independent statistician and finalised before any analysis takes place.

11.2. Description of the Statistical Methods

In accordance with CONSORT guidelines, we will record and report participant flow. Descriptive statistics of recruitment, drop-out, and completeness of interventions will be provided. Baseline variables will be presented by randomised group using frequencies (with percentages) for binary and categorical variables and means (and standard deviations) or medians (with lower and upper quartiles) for continuous variables. There will be no tests of statistical significance nor confidence intervals for differences between groups on any baseline variables.

11.2.1. Analysis of clinical outcomes

Analysis of the primary outcome will be performed using a generalised linear mixed effects model adjusting for stratification variables, and any baseline variables that are deemed to be highly prognostic of the outcome, will be used to determine the treatment effect and 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. Non-inferiority is claimed if the lower limit of the 95% confidence interval around the standardized effect size is -0.33. A P-value

for non-inferiority will also be calculated. Similar approach will be used for the other secondary outcomes.

11.2.2. Additional quantitative analyses

Treatment credibility, acceptability and experience scores will be calculated and compared for both treatment groups, using simple mean comparisons. Change in child symptoms and functioning on a sessional basis will be plotted to explore the trajectory of change in the OSI arm.

11.2.3. Qualitative analysis

Interviews will be audio-recorded and transcribed verbatim. Transcribed interviews will be analysed using an inductive thematic analytic approach (Braun & Clarke, 2006). Rather than relying on a pre-existing coding or theoretical framework, codes and themes will be data-driven. A number of strategies will be employed to enhance the credibility and methodological rigour of the analysis, including the use of reflexive practices in supervisory discussion and presentation of the analysis to a small group of expert researchers and therapists.

11.3. Sample Size Determination

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).

A sub-sample of up to 25-40 parents/carers and therapists from both arms will be involved in qualitative interviews after the treatment has been delivered in order to assess their experience of this treatment. Participants will be purposively sampled on the basis of demographics and treatment outcomes. We have previously found that this is sufficient for data saturation.

11.4. Analysis populations

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. A per-protocol analysis will also be carried out excluding those who have deviation from the protocol. Other analysis populations will be prespecified in the SAP.

11.5. Decision points

Due to the rapid nature of the trial there will be no interim analyses.

11.6. Stopping rules

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

11.7. The Level of Statistical Significance

P<0.05 will be used as the level of statistical significance.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

The availability of the outcome data for the primary outcome will be summarised by randomised group. The mixed effects model implicitly accounts for data missing at random, however the data missingness mechanism will be explored. Logistic regression models will explore any association between baseline characteristics and availability of the primary outcome. Missing primary outcome data will be reported overall and by randomised group. 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.

The response rates may differ between the intervention arms of the trial. A sensitivity analysis will be conducted that assume data are missing not at random (MNAR).

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the original statistical plan will be discussed and agreed with the Trial Steering Committee and their agreement will be minuted. Deviations will be explicitly reported in subsequent trial reports.

11.10. Health Economics Analysis

In order for a new intervention to be widely adopted in the NHS, it is necessary to assess not only its clinical effectiveness but also its cost-effectiveness, namely whether the new intervention is good value for money compared with current practice. In other words, the performance of an economic evaluation alongside this RCT will allow us to establish whether OSI+therapist support is worth doing compared with C-TAU and whether we are satisfied that the health care resources

required for OSI+therapist support to be made available to those who could benefit from it should be spent this way rather than some other way, i.e. C-TAU in this specific case. Therefore, the results of the economic evaluation will be invaluable to inform NHS decisions for treating child anxiety in such challenging circumstances and beyond.

The economic aspects of the study are summarised in this protocol. Details will be fully described in a health economics analysis plan (HEAP) (Thorn et al, 2021), which will be finalised before any analysis takes place.

The economic evaluation will comprise cost-utility analysis (CUA) as primary analysis, and cost-effectiveness analysis (CEA), as secondary analysis. They will be conducted from the NHS and personal services perspective (base-case analysis) as per NICE recommendations (NICE, 2022). A wider societal perspective (including parental health care resource use and work productivity and school impacts) will be adopted in sensitivity analyses. We will follow best-practice guidelines for conducting and reporting economic evaluation analyses (NICE, 2022; Husereau et al., 2022). Both an intention-to-treat and per-protocol approach will be adopted for primary and secondary analyses, as it is common in inferiority trials (Bosmans et al, 2008; Rhodes et al, 2014; European Medical Agency, 2005). Missing data will be imputed by use of conditional mean imputation for missing values deemed highly deterministic (e.g. online/ face-to-face therapist contacts), and multiple imputation for other variables (e.g. GP consultations) under the assumption of missing at random. In the cost-utility analysis, the health outcomes will be quality adjusted life years (QALYs) gained for the child (base-case analysis), and for the parent-child dyad (sensitivity analysis). QALYs will be derived from the collected measures CHU-9D (Stevens, 2012) for the child, and EQ-5D-5L (Dolan et al., 1995; NICE, 2022; Hernandez et al, 2020; Hernandez et al, 2017) for the parent. In the cost-effectiveness analyses (CEA) the outcomes will be percentage of school attendance and the CAIS-P. For each participant, components of treatment costs and other individual, family, and wider societal costs (as collected using the economic logs completed by therapists/ parents/carers) will be computed by multiplying units of resource use by their unit costs and then summed to obtain a total cost per patient. Unit costs for health, social care, and other resources will be mainly derived from local and national sources (PSSRU, 2020) and estimated in line with best-practice. Costs will be expressed in pounds sterling at current prices. Given the short time-frame of the trial and follow-up, discounting will not be applied to costs or effects. The incremental costs and effects will be reported using incremental cost-effectiveness ratios (ICERs), where appropriate, and presenting

cost-effectiveness acceptability curves (Fenwick, Marshall, Levy & Nichol, 2006). Sensitivity analyses to explore uncertainty surrounding ICERs will be also conducted.

12. DATA MANAGEMENT

A study specific Data Management Plan (DMP) will be developed for the Co-CAT trial outlining in detail the procedures that will be put in place to ensure that high quality data are produced for statistical analysis.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to,

- Parent/carer reported questionnaires
- Child reported questionnaires
- Therapist reported questionnaires
- Parent/carer and therapist interviews.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, each participant will be referred to by the trial participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Access to personally identifiable data will be restricted to a need to know basis. This will include the PI, co-investigators, research staff involved in data collection, therapists and clinical supervisors delivering the intervention.

Agreements will also be in place with external organisations (OSI Hosting provider and software developer, a transcription service) who will be data processors and will require access to personal data collected in this study. Oxford University Third Party Security Assessments (TPSA) will be

conducted for both organisations and they will be required to comply with the TPSA recommendation.

12.3. Data Recording and Record Keeping

The trial is being run as part of the portfolio of trials in the PC-CTU. The data management will be run in accordance with the PC-CTU SOPs, which are fully compliant with Good Clinical Practice (GCP). Data will be anonymised at the first instance possible and confidentiality will be maintained where required, the details of which will be outlined in the SAP and the DMP.

A PC-CTU data manager will be assigned to the study, as delegated by the CI, and will be responsible for overseeing the receiving, entering, cleaning, querying, analysing and storing of all data that accrues from the study by designated persons.

All participants (parent/carers, children, therapists) will be assigned a unique ID. A document that links the participant's personally identifiable data with the participant ID will be stored separately from all other research data. Therapist record will refer to the study id of the parent/career from the participating family so that data can be linked. Sentry will be used to ensure that record of participant contact details (email, telephone number, address) is stored separately from other data. Sentry is an online secure data entry system developed in-house at PC-CTU and hosted at Oxford. It is designed to collect sensitive data, such as participant contact details, and securely retain them separate from a trial's clinical data. Sentry can also act as a central participant portal to manage online eligibility, eConsent and ePRO - acting as an intermediary between the participant and the clinical databases. Sentry is accessed via a secure HTTPS connection and all stored sensitive data is encrypted at rest to AES-256 standards.

The main trial data will be entered directly into the participants' CRFs in an electronic format by the participant or trial team (using REDCap database via Sentry). The use of REDCap is compliant with Good Clinical Practice and guidelines such as 21 CFR Part 11 via differentiated user roles and privileges, password and user authentication security, SSL encryption, de-identification of Protected Health Information. Data will be hosted on network servers/drives which are maintained by University of Oxford MSD's and are backed up every 24 hours to and firewalls and authentication are in place to block any inappropriate access.

While all main trial data will be directly entered into electronic Case Report Forms (eCRFs), paper versions will be provided if access to the online CRF is not possible. In this case the original copy of the CRF will be returned to the study team and a copy will be held at the research site. All CRFs (electronic or paper) will be date stamped upon receipt. A full pre-entry review and electronic data validation for all data entered into the clinical database will be provided by study specific programmed checks. All paper data will be locked in secure cabinets and only the researchers will have access to the files. A separate database will be used to securely store all identifiable patient information required to contact patients and permit follow up. Access to this information will be strictly on a need to know basis and databases will be password protected on a secure server.

Routine sessional treatment data will be captured within OSI (for the OSI+therapist support arm only) and this will be available to the research team in pseudo-anonymised form via the OSI researcher portal. The pseudo-anonymised data will be regularly exported from OSI in CSV form and saved on the study restricted access OneDrive for merging (by study id) with the main trial data at the point of statistical analysis. The OSI online platform is based in the European Economic Area, and is compliant with NHS digital's requirements for data and security. As noted above, OSI will be subject to a University of Oxford TPSA and will be required to comply with recommendations.

Qualitative interviews will be audio recorded using an encrypted digital audio recorder. Recordings will be held temporarily on these audio-recording devices for no more than 24 hours before being securely transferred to a restricted access folder on the University of Oxford IT Network where they will be stored separately from all other research data in a restricted access OneDrive folder. The audio recording will be either i) transcribed by a member of the research team (manually or using Teams), or ii) sent securely via OneDrive to a transcriber with a contract with the university (and who has been subject to and found to comply with recommendations from a TPSA). The transcriber will be required to delete all audio files after returning the verbatim transcription to the research team.

Where Teams is used to transcribe (option i), the audio recording will be used to create a Teams transcript which will be automatically generated by Microsoft Teams in Nexus 365 STREAM, manually downloaded as a .vtt file to a temporary folder in the researcher's computer, uploaded to Microsoft STREAM VTT cleaner to remove all coding from the transcript, and the bare text of

the transcript then copied and pasted into a word document. The transcript will then be formatted, checked against the original audio, names removed and saved to a secure restricted access OneDrive folder. The recording on MS STREAM and .vtt file will then be deleted. Transcripts will be de-identified.

On completion of the trial and data cleaning, the study documentation will be transferred to a secure, GCP compliant archiving facility. Participants identifiable information will be kept for 6 months unless participants give permission for their information to be kept in order to be contacted about research after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for 3 years after the end of the study. Qualitative interview transcripts will be retained securely to support publications of findings from the study until they are no longer required. Prior to database lock, the Data Manager and the Trial Statistician will undertake a dataset review. Digitised consent/assent forms, and an electronic record of consent/assent completed online will be stored for 3 years after the study is complete, and then securely destroyed. The linkage information will be permanently destroyed at the end of the study. The only exception will be if participants (parents/carers) agree to be approached for future research, we will retain the consent form as the basis for retention of details and future approach. Those contact details will be held securely, separately from the research data, and will be kept updated. Audio-recordings will be stored until recordings have been transcribed verbatim, and transcriptions thoroughly checked. This means that audio files will be destroyed by the end of the study.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. In addition, a risk assessment will be carried out and provided to the CTRG before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities (e.g. monitoring of adverse events). A Trial Steering Committee will be convened to monitor study progress.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Regular monitoring will be performed according to a study specific Monitoring Plan, which will be reviewed by the CTRG prior to the initiation of recruitment. Data will be evaluated by the PC-CTU for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the trial manager (with support from Co-A, VR) will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13.3. Study Committees

A Trial Steering Committee (TSC) will be convened and will meet every 4 months (or as necessary in agreement with TSC) 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.

14. PROTOCOL DEVIATIONS

Study Operating Procedures (SOPs) will be in place, that align with Core Oxford University SOPs, describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

14.1. Serious Breach

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor will be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

15.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

15.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA and host institutions for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4. Other Ethical Considerations

This study involves collection of online questionnaire data from children (5-12 years). Although the child may choose not to provide any data directly (if they don't wish to complete any of the child report measures), both parent/carer consent and child assent is required for randomisation. Both parents and children will be provided with study information in both written and video forms and will have the opportunity to discuss the study and have questions answered prior to taking part. We anticipate that some participating children will need adult support to understand the study information and assent, and to complete the measures and we will provide parents/carers with guidance on how to do this with instructions available on the online system.

Participation in the study also introduces burden on participants from completion of questionnaires for research purposes. Participants will be reimbursed for their time participating in research specific elements of the study. The questionnaires that are administered are commonly used in clinical practice and research, however there is a possibility that some of the questions may cause some distress. We will encourage participants to raise these concerns with their clinical team and will provide participants with contact details for the research team for further discussion if required.

Potential for Distress

Completing the pre and post-treatment assessments may involve reflecting on distressing thoughts and feelings. These assessments are similar to those used in routine clinical practice, however for some children and parents they may cause a degree of distress or discomfort. The acceptability of all measures has been carefully considered with PPI representatives and we have used these measures in other similar studies. The voluntary nature of all assessments will be emphasised throughout and study researchers will be on the alert for families who appear unduly distressed, and will notify senior members of the study team immediately.

15.5. Reporting

The CI will submit an End of Study notification to the REC Committee, HRA, host organisation, Sponsor and funder. An Annual Progress report will also be submitted in the case of delays that mean the study runs for over 12 months.

15.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will be registered on a publicly accessible database and the trial information will be kept up to date during the trial. The CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

15.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

Procedures will be compliant with:
Data Protection Checklist https://researchsupport.admin.ox.ac.uk/policy/data/checklist
Practical Considerations https://researchsupport.admin.ox.ac.uk/policy/data/practical

15.8. Expenses and Benefits

No additional funding is provided to participants for travel expenses as all research activity will take place within the confines of normal care/ online.

Families will receive £10 as a thank you for completing extra questionnaires that they would not usually complete as part of routine care. Furthermore, parents/carers or clinicians who take part in the additional qualitative interview will receive a further £20.

16. FINANCE AND INSURANCE

16.1. Funding

This study has been funded by National Institute for Health and Social Care Research (NIHR) and the DHSC/UKRI COVID-19 Rapid Response Initiative and is managed by the Medical Research Council.

16.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

16.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

17. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the DHSC and UKRI COVID-19 Rapid Response Initiative, managed by the Medical Research Council. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. A summary of the study findings will be circulated at the end of the study to all participating clinical teams and families.

18. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial

19. ARCHIVING

Anonymised trial data will be made available open access on completion of the trial. Qualitative interviews will not be shared in this way due to the difficulties in fully anonymising the data.

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Appendix 1: SPIRIT schedule of enrolment, interventions and assessments

		Enrolment			Post-allocation		Close-out
			After consent	After randomisation	Treatment	14 weeks after randomisation	26 weeks after randomisation
Timepoint:			baseline			post-treatment	follow-up
ENROLMENT	Eligibility screen	X					
	Informed consent	X					
	Allocation			X			
	Demographic information		X				
INTERVENTIONS	OSI				X		
	C-TAU				X		
ASSESSMENTS							
CHILD REPORT							
Symptom measure	RCADS-C		X			X	X
Functional impairment	CAIS-C		X			X	X
PARENT REPORT							
Symptom measures	RCADS-P		X			X	X
	SCAS-P-8		X			X	X
Functional impairment	CAIS-P		X			X	X
	ORS		X			X	X
Co-morbid problems	SDQ-P		X			X	X
Pandemic Anxiety Scale	PAS		X			X	X
Treatment acceptability	Credibility and Expectation of Improvement scale			X		X	
Heath economics	CSRI		X			X	X
	EQ-5D-5L- P		X			X	X
	CHU-9D (YP proxy)		X			X	X
<u>OSI+therapist support</u> ARM ONLY Measures collected during treatment (parent only)	RCADS-P				X		
	SCAS-P-8				X		
	CAIS-P				X		
	ORS				X		
	SRS				X		
	GBOs				X		
Qualitative interviews						X (subgroup of participants interviewed once each between 14 and 26 weeks)	X (subgroup of participants interviewed once each between 14 and 26 weeks)

Therapist Logs					X	X	X

Appendix 2: Flowchart of Trial Procedures