OPTYC: Online PTSD Treatment for Young People and Carers

ISRCTN: ISRCTN16876240

Statistical Analysis Plan

Version 1.0: 24/09/2021

Refers to Protocol Version 1.4, filename: OPTYC_Protocol_v1.4_26.11.2020.docx

Signatures

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1 Table of Contents

2 Amendments to the SAP

Date	SAP version	Protocol version and date	Reason for change/Amendment made
	V1.0	1.4 26.11.2020	Initial version

3 Description of the trial

OPTYC is a two-arm parallel groups 1:1 randomised early phase feasibility trial which aims to evaluate an Internet-delivered Cognitive Therapy programme for the treatment of PTSD in adolescents.

3.1 Principal research objectives to be addressed

The aim of OPTYC is to conduct an early phase RCT to evaluate an Internet-delivered Cognitive Therapy (iCT) programme for the treatment of Post Traumatic Stress Disorder (PTSD) in adolescents.

The objective of the RCT is to: provide feasibility data on acceptability, compliance, retention, and delivery and other procedural uncertainties; and to provide exploratory point estimates of the effect sizes (and confidence intervals) of iCT on the primary and secondary clinical endpoints. These data will indicate whether a larger RCT is warranted. Summary statistics from participants allocated to the iCT arm will be used to inform a larger RCT.

3.2 Progression to a full trial

Progression from feasibility to a future definitive RCT is warranted is based on the criteria detailed below. A traffic light system will be used with thresholds for each feasibility criteria of 'Green', 'Amber', and 'Red'. 'Green' would indicate the future definitive trial is likely feasible; 'Red' would indicate that it is likely not feasible; and 'Amber' would indicate that it may be feasible if appropriate changes were made.

1. *Percentage of eligible patients consenting to the early stage RCT*

   Green = 65% or more; Amber = 50% or more; Red = below 50%.

2. *Percentage of randomised patients providing outcome data (including weekly measures) on a PTSD measure*

   Green = 90% or more; Amber = 80% or more; Red = below 80%

3. *Data completeness: Percentage of trial completers providing complete data on a PTSD measure*

   Green = 90% or more; Amber = 80% or more; Red = below 80%

If a definitive trial is likely to be feasible based on the above criteria, we would then examine the initial signal of clinical effect to determine whether adjustments to the intervention are needed before progression. We acknowledge the difficulty of estimating accurate statistical quantities from data gathered in a small early stage trial such as this one. We will therefore examine point estimates of between group effect sizes (and their confidence intervals) on a continuous outcome measure of PTSD symptoms.

4. *Effect size of iCT vs WL on the secondary outcome* CPSS

   Green= d >0.8, Amber = d >0.5, Red = d <0.5

Green: changes to the intervention not required; Amber: minor changes to the intervention may be needed; Red: changes to the intervention needed before progression.

3.3 Trial design including blinding

OPTYC is a two arm, parallel group, 1:1 randomised early phase feasibility study. The arms of the study are Internet cognitive therapy (iCT), and Wait List (WL).

3.3.1.1 Blinding

All assessors of the primary and secondary clinical outcomes at follow-up at 16 weeks will be blind to treatment allocation. Assessors will not need to be blind at the 6 week and 38 week follow up assessments. Dr Kim Goldsmith will also be blind (for all time points and all databases, including baseline data, safety data, and primary and secondary clinical outcomes) to treatment allocation. Analysis of the trial by arm will occur after the analysis plan is signed off, and the database (including 38 week follow-up) is locked. Unblinding of the senior trial statistician will occur after the initial draft of the statistical analysis report is generated.

All other members of the study team, PMG, will be unblind to treatment allocation. Participants in the trial will be unblinded to treatment allocation.

3.4 Method of allocation of groups

Following the baseline assessment, individual participants will be randomised to receive iCT, or WL at a 1:1 ratio. Randomisation will be carried out by the King's Clinical Trials Unit (KCTU) using a web-based service in accordance with a standard operating procedure and held on a secure server. The randomisation allocation will utilise minimisation with a random component. Minimisation factors will be:

1. Sex;
2. Baseline symptom severity assessed by the CPSS (low: <51, high: ≥51);

For each participant, an unblinded member of the study team will request the randomisation allocation by supplying the participant's PIN and stratification factors via the KCTU web interface. Randomisation allocations will be sent to the unblinded RA via email.

3.5 Duration of the treatment period

The interventions given to participants in the iCT arms will be delivered over 12 weeks. Participants in the wait list control arm will wait for 16 weeks before being offered iCT or, if preferred and if clinics are open and functioning as usual at the time, participants can opt for face to face cognitive therapy.

3.6 Frequency and duration of follow-up

Participants will complete follow up measures at baseline, and 6, 16, and 38 weeks post randomisation. The date of randomisation will be considered day 1 of follow up. Follow up at 38 weeks is completed for participants in the iCT arm only. For participants in the iCT arm CRIES-8 is collected weekly. Full details of the schedule of assessment are given in appendix 1.

3.7 Eligibility screening

3.7.1 Inclusion criteria

- Participant is aged 12-17 years old.
- Main presenting problem is PTSD and there is a not a co-morbid problem that would preclude treatment of PTSD. Potential PTSD will be diagnosed using CAPS-CA-5. Potential co-morbid disorders that would preclude treatment of PTSD (for example severe depression, severe OCD) will be assessed by the online DAWBA (Goodman et al., 2000) and by face-to-face clinical interview.
- PTSD symptoms related to a single trauma.
- Participant speaks English to a level that allows therapy without the need for an interpreter, and reads English to a level that allows independent use of iCT.
- Participant has access to compatible smartphone and larger computing device (e.g. laptop, desktop computer, iPad) with internet access.

3.7.2 Exclusion criteria

- Brain damage, assessed by clinical interview with parents / carers.

- Intellectual disability, assessed by clinical interview with parents / carers.
- Pervasive developmental disorder or neurodevelopmental disorder, assessed by clinical interview with parents / carers.
- Other psychiatric diagnosis that requires treatment before PTSD, determined by clinical interview and questionnaires.
- Moderate to high risk to self, assessed in clinical interview.
- Ongoing trauma-related threat, assessed in clinical interview.
- Started treatment with psychotropic medication, or changed medication, within the last 2 months, assessed in clinical interview.
- Currently receiving another psychological treatment, assessed in interview.
- Has previously received TF-CBT in relation to the same traumatic event that they are currently seeking treatment for.

3.8 Outcomes

3.8.1 Feasibility outcomes

Referral route

1. The total number of young people referred to the trial by (i) schools, (ii) CAMHS, or (iii) GP or self-referral

School screening

2. Number of young people screened in schools, and of these, the proportion who are considered to be eligible at school and proceed to a phone call with family.
3. Number and proportion of young people in schools scoring above cut-off on a validated screening questionnaire (a score of ≥17 on the Children's Revised Impact of Event Scale, CRIES-8; (Dyregrov & Yule,1995, Perrin et al., 2005), relative to the number of young people screened in schools.
4. The number and proportion of young people in schools who score above cut-off on the CRIES-8 but decline further participation with the trial (relative to those scoring above cut-off).
5. The number and proportion of young people in schools who score above cut-off on CRIES-8 and consent to further assessment but are deemed ineligible at baseline assessment (relative to those deemed eligible at baseline assessment).

Eligibility assessments and numbers consenting

6. Number of assessment appointments offered to participants (via any referral route).
7. Number and proportion of assessment appointments attended by participants, relative to the number of appointments offered, reported by referral source (schools, CAMHS, GP referral, and self-referral).
8. Reasons for not attending assessment appointments (count and percentages) reported by referral source (schools, CAMHS, GP referral, and self-referral).
9. Number and proportion of young people who, at the baseline assessment, consent to participation in the trial (number consented / number attended assessment). Reasons for not consenting if known (count and percent).
10. Number and proportion of young people eligible for the trial after baseline assessment (number eligible at baseline interview/number assessed for eligibility at baseline interview).
11. Number of young people who are randomised, and proportion of consented young people who are randomised (number randomised / number consented).

Follow up

12. Reasons for withdrawing from the trial if known.
13. Number retained in study at 16 weeks (post-treatment) and at 38 weeks (follow-up), and proportions of those who start treatment that are retained (number retained / number started, and number retained/number randomised).

We will also report the progression criteria given in section 3.2.

3.8.2 Adherence metrics

In iCT we will report:

14. Number of times logged into the programme per week and in total.
15. Time spent logged in per week and in total.
16. Number of modules completed in total and according to device used (phone, tablet, computer).
17. Number of therapist phone calls attended per week and in total, and the number of missed phone appointments.
18. Time spent on phone calls per week and in total.
19. Number of messages to / from therapist per week and in total.

20. Number and proportion of young people who (number starting treatment/number randomised).
21. Number of weeks of therapy completed.
22. Reasons for dropping out of treatment if known.

3.8.3 Primary clinical outcome measures

- Presence of PTSD according to DSM-5 at 16 weeks post-randomisation, ascertained using the Clinician Administered PTSD Scale for Children and Adolescents CAPS-CA-5 (Pynoos et al., 2015), administered by trained reliable raters, blind to treatment.

3.8.4 Secondary clinical outcome measures

At 16 weeks post-randomisation:

- Continuous measure of PTSD symptom severity on the CAPS-CA-5 (1)
- Child Post Traumatic Stress Scale (CPSS-5) (2)
- Children's Revised Impact of Event Scale (CRIES; (3))
- Revised Children's Anxiety and Depression Scale RCADS-C; (4)) (young person completion)
- Revised Children's Anxiety and Depression Scale (RCADS-P(4)) (carer completed)
- Strength & Difficulties Questionnaire (SDQ-P; (5))

At 38 weeks post-randomisation in iCT and FtF CT arms only

- Child Post Traumatic Stress Scale (CPSS-5)
- Children's Revised Impact of Event Scale (CRIES)
- Revised Children's Anxiety and Depression Scale RCADS-C) (young person completion)
- Revised Children's Anxiety and Depression Scale (RCADS-P) (carer completed)
- Strength & Difficulties Questionnaire (SDQ-P) (carer completed)

3.8.5 Mediation outcomes

- Child Post Traumatic Cognitions Inventory (CPTCI, (6))
- Trauma Memory Quality Questionnaire (TMQQ; (7))

- Trauma Related Rumination items (8)

Details of the scoring for clinical outcomes is given in appendix 3.

The acceptability outcomes mentioned in Section 3.2.2 of the protocol V1.4 are qualitative outcomes, and those in Section 3.2.6 are health economic outcomes. These outcomes will not be analysed by the statisticians, but rather by other members of the trial team; these outcomes are not referred to further in this SAP.

3.8.6 Adverse events

Adverse events are defined as any untoward occurrence in a trial participant, including events that are not necessarily caused by or related to trial procedures. The following are listed as expected adverse events:

- Self-harm not requiring medical attention (e.g. minor scratching)
- Increase in suicidal ideation (assessed by clinical interview)
- Worsening of PTSD symptoms (defined as 7-point increase in CRIES-8)

3.8.7 Serious Adverse events

Serious adverse events (SAE) are defined above as any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongs existing hospitalisation;

Results in persistent or significant disability or incapacity.

They may represent a worsening of AE symptoms. For example:

- Self-harm requiring medical attention e.g. cutting with a blade
- Suicidal behaviours or suicide attempts e.g. overdose of medication

3.9 Data collection

- Feasibility outcomes (Section 3.8.1, outcomes 1-13); will be collected by the study team.
- Adherence metrics (Section 3.8.2) will be collected by the study team or via the intervention app/website. Outcomes 14, 15, 20 and 21 will be collected via the app, outcomes 16-19, and 22 will be collected by the study team with the addition of information on devise used for outcome 16 coming from the app.
- CAPS-CA-5 is collected via interviews with the study team. Baseline interviews will be conducted by unblind members of the study team. Post-treatment interviews will be conducted by blinded outcome assessors.

- Other secondary outcomes at 16 weeks (excluding the CAPS-CA-5) and mediation outcomes are completed by participants or their parents/carers using an online CRF hosted in Qualtrics and transferred to an SPSS database.
- Follow-up data collection at 38 weeks will be collected via online CRF hosted in Qualtrics and transferred to an SPSS database.

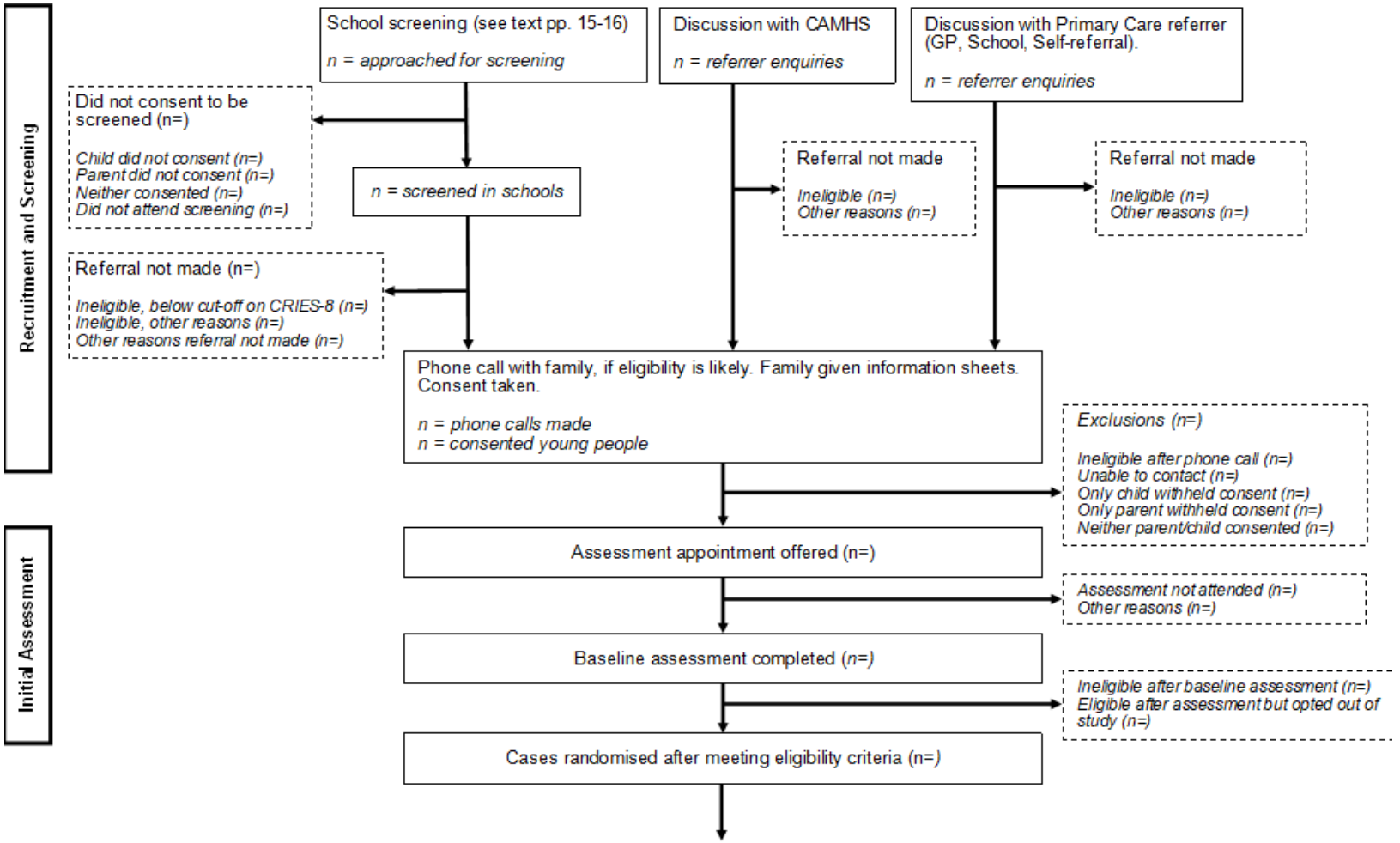
3.10 Sample size estimation

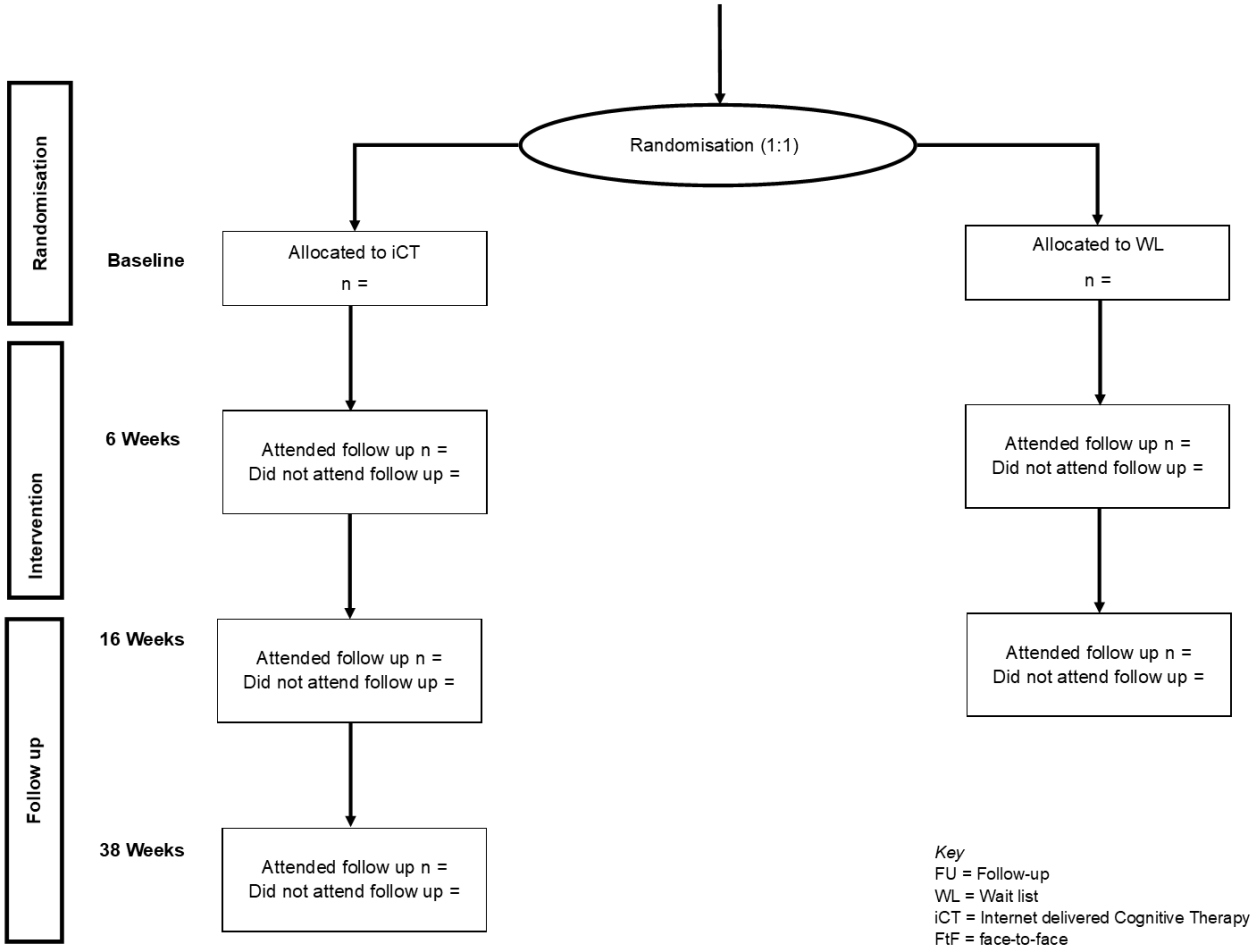
We will recruit 17 participants in the iCT arm, and 17 participants in WL. In our previous RCTs of face-to-face CT, we had 4% drop-out across both arms, but we have conservatively allowed for approximately 20% drop-out, to give at least n = 14 at post-treatment in each arm. An early stage trial of this size will be sufficient to gather meaningful feasibility data on acceptability, compliance, retention, and delivery. For example, with 34 participants, we will be able to estimate the recruitment rate to within approximately 34% ie. if we recruit 2 per month the 95% confidence interval will be 2 +/- 2*0.34 = (1.32 to 2.68)(9).

The trial will also provide estimates of statistical quantities for the primary and secondary outcomes in each arm. These will be used to help with sample size calculations for a larger definitive trial of iCT versus FtF-CT, utilising our previous trial data and the wider literature comparing FtF-CT versus WL.

Power calculations are not typically used to determine sample size for feasibility studies. Therefore, we acknowledge an insufficient sample size to allow definitive between-group comparisons in this early stage RCT (10,11).

Figure 1. Template CONSORT diagram for OPTYC trial




Randomisation
Intervention
Follow up
Randomisation (1:1)
Baseline
Allocated to iCT
n =
Allocated to WL
n =
6 Weeks
Attended follow up n =
Did not attend follow up =
Attended follow up n =
Did not attend follow up =
16 Weeks
Attended follow up n =
Did not attend follow up =
Attended follow up n =
Did not attend follow up =
38 Weeks
Attended follow up n =
Did not attend follow up =
Key
FU = Follow-up
WL = Wait list
iCT = Internet delivered Cognitive Therapy
FtF = face-to-face

4 Data analysis plan – Data description

4.1 Recruitment and representativeness of recruited patients

A CONSORT flow chart will be constructed, see figure 1 for an outline.

4.2 Baseline comparability of randomised groups

Baseline descriptions of participants will be reported by treatment arm and overall: means and standard deviation, median lower quartile, upper quartile, or numbers and proportions as appropriate. We will not conduct significance tests to evaluate differences between trial arms.

4.3 Loss to follow-up and other missing data

The number and proportion of participants missing each variable will be summarised overall, in each arm and at each time point. The number and proportions actively withdrawing from the trial will be summarised overall and by trial arm, with reasons for active withdrawal from the trial summarised.

4.4 Adverse event reporting

We will report the total number, and the number and percentage of participants experiencing Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR).

4.5 Descriptive statistics for clinical outcome measures

The primary outcome (PTSD caseness at 16 weeks post-randomisation) will be summarised with frequencies and proportions overall and by treatment arm. Secondary outcomes will be summarised with means and standard deviations overall and by treatment arm.

4.6 Reliable improvement and reliable deterioration

At each time point, and in each arm we will report the numbers and proportion achieving a reliable improvement or reliable deterioration for the secondary outcomes CPSS and CRIES. For the CRIES participants will be defined as having a reliable change if their score from baseline changes by at least 11.92. For CPSS a reliable change is defined as a change from baseline of at least 14.87. Reliable changes in the direction of better outcomes will be considered reliable improvements and in the direction of worse outcomes reliable deterioration.

5 Data analysis plan

5.1 Feasibility outcomes, adherence outcomes and progression criteria

Feasibility and adherence outcomes will be summarised using descriptive statistics: number and proportion, mean and standard deviation as appropriate. Overall summaries will be provided for outcomes relating to referral route, school screening, eligibility assessments and consent. Feasibility outcomes relating follow-up will be presented overall and separately by arm. The progression criteria will also be reported, details on the denominators and numerators for each criteria are given in appendix 2.

For outcomes measuring adherence the number of weeks of therapy will be defined as the number of weeks between first log on to the last log on or final therapist support call. This will be used as the denominator where we are reporting adherence measures 'per week'. Participants will be classified as starting treatment if they log on to the app at least once.

We will provide break outs of outcomes relating to app use showing app use within the intervention period (within 12 weeks of randomisation) and outside of this period.

5.2 Preliminary estimation of clinical outcome treatment differences

The aim of the analysis of treatment differences, including the primary outcome, is to give an indication of the potential range of effect sizes from iCT. We will report estimates and 95% confidence intervals to describe the precision in any estimates obtained. As the trial is not powered to detect differences between arms we are not reporting p-values and estimates obtained will not be used to claim strong evidence for the effectiveness or ineffectiveness of the intervention.

Analysis will follow a modified intention-to-treat principle: all eligible, randomised patients with a recorded outcome (ie. outcome is not missing) will be included in the analysis, and analysed according to the treatment to which they were randomised.

For all outcomes we will report treatment effect estimates, 95% confidence intervals comparing iCT with WL. As this study is not powered to detect differences between arms we will not report p-values. Outcomes measured at 38 weeks are measured in one arm only and will be summarised with descriptive statistics.

All analysis of clinical outcomes will adjust for the minimisation covariates using the following categories: Sex (male, female), PTSD severity at baseline (low, high).

5.2.1 Analysis of primary clinical outcomes

The primary outcome will be analysed using logistic regression, treatment effects will be reported using adjusted odds ratios. Covariates will be treatment allocation and the minimisation factors sex and PTSD severity at baseline.

5.2.2 Analysis of secondary clinical outcomes

5.2.2.1 Measured at 16 weeks

All secondary outcomes measured in both arms at 16 weeks only will be analysed using a linear regression model adjusting for treatment allocation, the baseline measure of the respective outcome and the minimisation factors sex and PTSD severity at baseline.

For all secondary outcomes treatment effects will be reported using adjusted mean difference and the 95% confidence interval. To avoid normality assumptions 95% confidence intervals will be calculated using bootstrapping. Bootstrapping will be implemented using residual resampling and we will report bias corrected and accelerated confidence intervals using 1999 bootstrap resamples. To address Progression Criterion 4, we will also calculate a Cohen's d effect size for the continuous CPSS and CRIES secondary outcome measures as outlined in Appendix 2.

5.2.2.2 Measured at 38 weeks

We will report mean and standard deviation for data collected at 38 weeks. No treatment effects will be presented as these data are collected in the iCT arm only.

5.2.2.3 Additional follow up in the wait list arm for participants who receive the intervention

Post intervention data collected on participants in the wait list arm who go on to receive the intervention is being collected for exploratory reasons and will not be used to assess efficacy. This data will not be analysed by the trial statisticians.

5.3 Per protocol analysis

In addition to the main analysis described above we will conduct two per protocol analyses for the primary outcome, and the CPSS-5 and CRIES-8 secondary outcomes at 16 weeks. For each outcome the main analysis will be repeated separately in the two per-protocol populations; participants receiving the minimum therapy needed to achieve benefit and the broader per protocol population. Participants will be included in the analysis if they have a recorded outcome and meet the respective per-protocol definition. Results from the per-protocol analysis will be considered secondary to results of the primary analysis.

5.3.1 Minimum therapy needed to achieve benefit

Participants will be considered to have met the per-protocol definition of completing the minimum therapy needed to achieve benefit if they either completed the following modules or it was agreed with the therapist and supervisor that a module was not needed.

a. What is PTSD
b. Reclaiming life
c. It's Understandable
d. Your story
e. Hotspots
f. Updating your story

5.3.2 Broader per-protocol population

In addition to participants completing the minimum therapy needed to achieve benefit we will consider a broader population. This will include participants who, in addition to meeting the criteria for “Minimum therapy needed to achieve benefit”, also completed the module on triggers (or it was agreed with the therapist and supervisor that the trigger module was not needed).

5.3.3 Assessing module completion

Whether a module has been completed for a particular participant will be agreed by the therapist and supervisor and recorded in the trial database.

We will not use the automatic module completion indicator in the app data as participants may complete all the components of a module which are necessary for clinical reasons without completing all the actions in the app required for the app to register module completion.

5.4 Missing data

For each variable we will report the number (%) with complete data.

5.4.1 Partially completed scales

For RCADS and SDQ we will use the missing value guidance provided with the scales (see appendix 3 for details). For all other measures, scales will be pro-rated for an individual if 20% or fewer items are missing. For example, in a scale with 10 items, prorating will be applied to individuals with 1 or 2 items missing. The average value for the 8 or 9 complete items will be calculated for that individual and used to replace the missing values. The scale score will be calculated based on the complete values and these replacements. If more than 20% of items are missing the scale will be treated as missing.

5.4.2 Missing baseline covariates

Missing baseline measures of secondary clinical outcomes will be handled using mean imputation. The missing measure will be imputed as the mean at baseline for that measure across both treatment arms (13).

No missing data are expected in the minimisation variables as these must be completed for randomisation to occur.

5.4.3 Missing outcome data

We will only include participants in the analysis if they have a completed outcome. Participants with missing outcome data will be excluded from the analysis. The analysis assumes missing data is missing at random (MAR) given the covariates included in the models.

5.5 Sensitivity analyses

There are no planned sensitivity analysis.

5.6 Planned subgroup analyses

There are no planned subgroup analyses.

5.7 Mediation analysis

An exploratory mediation analysis will be carried out to assess how much of the effect of the iCT vs WL on the primary clinical endpoint (PTSD caseness measured at 16 weeks post-randomisation) is transmitted via the Child Post Traumatic Cognitions Inventory score (CPTCI), the Trauma Memory Questionnaire (TMQQ), and items relating to rumination. Mediators are measured at 6 weeks post-randomisation. The indirect effect will be calculated following the method of Vanderweele (14) using suitable a software package, such as the Stata command paramed(15). We will use a logistic regression model for the outcome and a regression model for the mediator. We will assume no treatment mediator interaction. The *a* path (regression parameter for the effect of treatment on the mediator), *b* path (regression parameter for the effect of mediator on the outcome), total, direct, and indirect effects of treatment allocation on 16-week PTSD caseness (0/1) will be presented, along with associated 95% confidence intervals. Confidence intervals for the indirect effect will be estimated using the percentile bootstrap procedure(16).

5.8 Interim analysis

There are no formal interim analysis planned.

6 Software

6.1 Data collection

The bespoke randomisation system for the trial is provided by KCTU. All data collected via the trial team will be saved in an SPSS database. Data collected automatically via the app will be received in a .csv file. Please see the protocol for more details on data collection, storage and security.

6.2 Analysis

Unless otherwise specified analysis will be carried out using Stata 16 or R.

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Appendix 1: Schedule of assessment

MEASURE	STUDY PERIOD					
	Screen 0-1 weeks	**Pre** 0 weeks	**Weekly** (*iCT only*)	**Mid** 0+ 6 weeks	**Post** 0+ 16 weeks	**Follow-up** 0+38 weeks (*iCT only*)
ENROLMENT						
Eligibility screen	x					
Provide study information	x					
Gain informed consent		x				
ONLINE ASSESSMENT						
DAWBA		x				
INTERVIEW						
DEMOGRPAHIC INTERVIEW		x				
CAPS-CA-5		x			x	
CGAS		x			x	
ADOLESCENT QUESTIONNAIRES						
CPSS-5		x			x	x
CRIES-8		x	x	x	x	x
RCADS-C		x			x	x
CPTCI		x		x	x	x
TMQQ		x		x	x	x
Rumination items		x		x	x	x
CHU-9D		x			x	x
Adverse events				x	x	x
CARER QUESTIONNAIRES						
SDQ-P		x			x	x
RCADS-P		x			x	x
CA-SUS		x			x	x
Adverse events				x	x	x
QUALITATIVE INTERVIEWS						
Adolescents					x	
Carers					x	
Therapists					x	

Notes:

DAWBA Development And Well-Being Assessment (online assessment)

CAPS-CA-5, diagnostic interview for PTSD

CGAS, clinician rated global measure of functioning

CPSS-5, severity of PTSD symptom (27 items)

CRIES-8, severity of PTSD (8 items)

RCADS-C, severity of anxiety and depression (47 items)

CPTCI, appraisals potential mediator (10 items)

CHU-9, health state preferences (quality of life) (9 items)

SDQ-P, emotional and behavioural problems (33 items)

RCADS-P, severity of anxiety and depression (47 items)

CA-SUS, service use and costs (50 items)

Appendix2: Rules for deriving the progression criteria

We will report numerator, denominator and percentage for progression criteria 1-3. These will be calculated as follows:

1. Percentage of eligible patients consenting to the feasibility RCT

- Numerator: the number of young people who sign a patient consent form
- Denominator: the number of young people who complete a baseline assessment and satisfy all inclusion and exclusion criteria.

2. percentage of randomised patients providing outcome data (including weekly measures) on a PTSD measure

- Numerator: the number of trial participants with a completed at least one of CAPS-CA-5, CPSS-5, CRIES-8 at any time point, or completed at least on weekly follow up assessment of the CRIES-8.
- Denominator: we will use the total number of randomised patients.

3. Data completeness - percentage of trial completers providing complete data on a PTSD measure –

- Numerator: the number of trial participants with a completed at least one of CAPS-CA-5, CPSS-5, CRIES-8 at 16 weeks.
- Denominator: Total number of participants attending 16 week follow-up

4.Effect size [Cohen's D] of iCT vs WL on the secondary outcome CPSS

Cohen's d will be calculated by dividing the treatment effect and confidence limits for by the standard deviation of CPSS at baseline.

Appendix 3: Deriving clinical outcomes

Outcome acronym	Number of items contributing to score	Scoring	Min-Max	Scores for better outcomes
CAPS-CA-5 (binary)	n/a	Derived outcome entered into database	0-1	0
CAPS-CA-5 (continuous)	20	Sum of items B1-B5, C1-C2, D1-D7, E1-E6	0-80	Lower
CPSS-5	20	Sum of items 1-20	0-80	Higher
CRIES-8	8	Sum of all items	0-40	Lower
RCADS	47	Sum of all items	0-141	Lower
SDQ – total score	20	Sum of all items with exception of prosocial scale (items 1, 4, 9, 17, 20). Reverse scoring items 7, 11, 14, 21, 25.	0 – 40	Lower
CPTCI,	10	Sum of items	10 - 40	Lower
TMQQ	11	Sum of items	11-44	Lower
Trauma Related Rumination	3	Sum of items	4-12	Lower

Partially completed scaled

The SDQ and RCADS scoring instructions contain specific provisions for partially completed scales. We will follow these rules when deriving outcomes.

SDQ

Scores may be prorated by subscale if 3 out of 5 items in the subscale are completed. Missing items are imputed as the mean of the competed items of the respective subscale. Items corresponding to each subscale are:

- Emotional problems 3,8,13,16,24
- Conduct problems 5,7,12,18,22
- Hyperactivity 2,10,15,21,25
- Peer problems 6,11,14,19,23

- Prosocial 1,4,9,17,20

RCADS

Subscales may be prorated if no more than 2 items are missing. Missing items are imputed as the mean of the complete items in the respective subscale. Items which make up each subscale are:

- Social Phobia 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