Pragmatic RAndomised controlled trial of a Trauma-Focused Guided Self Help Programme versus InDividual Trauma-Focused Cognitive Behavioural Therapy for Post-Traumatic Stress Disorder (RAPID)

PROTOCOL

Sponsor:	**Cardiff University**
Sponsor ref:	**SPON 1545-16**
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor:			
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Name	**Position**	**Signature**	**Date**
Director:			
Professor Monica Busse			
Name	**Signature**		**Date**
Chief Investigator:			
Professor Jonathan Bisson			
Name	**Signature**		**Date**

General Information This protocol describes the RAPID clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

Contact details – Chief Investigator & Co-Investigators

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Trial Co-ordination:

The RAPID trial is being coordinated by South East Wales Clinical Trials Unit (CTU), a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit which is part of the Cardiff University Centre for Trials Research (CTR). This protocol has been developed by the RAPID Trial Management Group (TMG).

For **all queries** please contact the RAPID team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or Co-Investigators.

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Clinical queries:

Clinical queries

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All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to the CTR safety team within 24 hours of becoming aware of the event.

Contact details

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Contents

Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
AUDIT-O	Alcohol Use Disorders Test
CA	Competent Authority
CAPS-5	Clinician Administered PTSD Scale
CF	Consent Form
CI	Chief Investigator
CMHT	Community Mental Health Team
CRF	Case Report Form
CSSRI-EU	Client Socio Demographic and Service Receipt Inventory (European Version)
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
CVUHB	Cardiff and Vale University Health Board
DMEC	Data Monitoring and Ethics Committee
DSM-5	Diagnostic and Statistical manual of Mental Disorders (5th edition)
EMDR	Eye Movement Desensitisation and Reprocessing
EQ-5D-5L	Euroqol-5D
EUCTD	European Union Clinical Trials Directive
GAD-7	General Anxiety Disorder -7
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GSES	General Self-Efficacy Scale
GSH	Guided Self Help
GP	General Practitioner
HB	Health Board
HCL	Healthcare Learning
HE	Health Economics
HTA	Health Technology Assessment
IAPT	Improving Access to psychological Therapies
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IES-R	Impact of Event Scale (Revised)
ISI	Insomnia Severity Index
ISRCTN	International Standard Randomised Controlled Trial Number
IU	International Unit
KTP	Knowledge Transfer Partnership
LEC-5	Life Events Checklist
MRC	Medical Research Council
MSPSS	Multidimensional Scale for Perceived Social Support
NCMH	National Centre for Mental Health
NCT	National Clinical Trial
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health & Care Excellence
NLI	No Local Investigator
NPSA	National Participant Safety Agency

NRR	National Research Register
PCT	Primary Care Trust
PHQ-9	Patient Health Questionnaire – 9
PI	Principal Investigator
PIAG	Participant Information Advisory Group
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PTCI	Post-Traumatic Cognitions Inventory
PTSD	Post-Traumatic Stress Disorder
QA	Quality Assurance
QALY	Quality-adjusted Life Years
QC	Quality control
QL (QoL)	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage
SEWTU	South East Wales Trials Unit
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TFCBT	Trauma Focused Cognitive Behavioural Therapy
TFPT	Trauma Focused Psychological Therapy
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSQ	Trauma Screening Questionnaire
WSAS	Work and Social Adjustment Scale

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
Minor Amendment 1	1.1	6th February 2017	Trial schema flow chart on page 14 amended to show the correct numbers under 'allocation'. REC reference added on page 0
Substantial Amendment 1	2.0	11th April 2017	Trial Statistician changed from Mark Kelson to Tim Pickles Changed wording of ineligibility criteria from 'Previous completion of a course of Trauma-focused Cognitive Behavioural Therapy (TFCBT) for PTSD' to 'previous completion of a course of trauma-focused psychological therapy for PTSD'. Added in re-checking of inclusion criterion 2 (PTSD symptoms to a single traumatic event) and exclusion criteria 7 (active suicide risk) at baseline interview. Minimisation criteria changed to gender only and stratification by research centre. Clarified Life Events Checklist is LEC-5 Changed 'all CRFs will be completed electronically' to 'where possible, all CRFs will be completed electronically'.

			Removed sentence stating we will conduct exploratory analysis of the effect of pain and educational attainment – these were an artefact of a previous document. Changed requirement for therapists to complete training case with actual service user to the possibility of training with a mock service user (role play). Added that the TSC has agreed we will have a DMC Clarified that the GP will be informed the participant is taking part in RAPID (this is in the PIL but not explicit in protocol V1.1). Also that ineligible or non-consenting patients will be referred back to the service that referred them, or to their GP. Clarified that we will record at least one therapy session for each participant to enable fidelity checking
Substantial Amendment 2	V3.0	24th October 2017	Changed the Trial manager name from Claire Bartlett to Katy Addison as change in staff. Also amended the contact number to **02920 687 522** Table 1 has been corrected to reflect that the CAPS5 is taken at the 16 wk follow-up as well as the 52 wk follow-up. Section 21.1 Added in that protocol has been approved by Wales REC 3 Section 13.2 Changed the wording so that therapists should report incidences of participant self harm/harm to others by email,

			rather than completing a separate CRF. Addition of Client Satisfaction Questionnaire (CSQ-8), 16 weeks post-randomisation. This is a brief 8-item Likert Scale to evaluate treatment satisfaction. The following sections have been updated accordingly: 2, 5.4, 12.1, 15.1. References 44 and 51 added to reference list. Reference 39 has been corrected, previously it showed a bookmark reference now the complete reference to the EuroQol group has been added. Another column has been added to Table 2 to show the 52 wk follow-up measures separate to the 16 wk follow-up measures (previously they were combined in one column). The Trial Schema and the Participant Flow Diagram have been amended to clarify that the second qualitative interviews will take place after the 16 week follow-up. Change of wording from Trauma Focused Cognitive Therapy to Trauma Focused Cognitive Behaviour Therapy with resulting change in acronym from TFCT to TFCBT. Where the term CT-PTSD or CT for PTSD has been used, this has also been changed to Trauma Focused Cognitive Behaviour Therapy or TFCBT. The following Sections have been updated accordingly: Glossary of Abbreviations, 11.1.2, 11.2, 14.3, 15.3. Added in that a limited amount of merchandise will be given to referrers to remind them about RAPID (section 9.1) The intention to carry out a survival analysis

			on self-report symptom outcomes has been removed from section 15.1 and replaced with a plan to carry out hierarchical modelling and co-variance structures of the IES-R data. The Process Evaluation section has been amended to clarify that both therapists and patients will be invited to take part in qualitative interviews, and that other stakeholders will also be interviewed (section 15.4.
Substantial Amendment 3	V4.0	12th January 2018	Signature page: corrected spelling of Chief Investigator's first name from John to Jonathan Contact Details of Chief Investigator and Co-investigators: Amended Mark Kelson's email from his previous Cardiff address to M.J.Kelson@exeter.ac.uk, and his job title from Research Fellow – Statistics to Senior Lecturer and Statistician. Section 2. Synopsis and Section 8.2, Exclusion Criteria: Amended the exclusion criterion 'Psychosis' to 'Current psychosis'. Section 7. Site and Investigator Selection: Addition of Edinburgh as a location for a centre. Section 7: To reflect that we now have one site in London and will have four in Edinburgh. 'Each centre will aim to recruit approximately three sites' has been amended to 'Within each centre up to four sites will be recruited.' Synopsis (Secondary Objectives): Addition of Measured 3 weeks from start of treatment and 16 weeks post-randomisation: Therapeutic alliance as measured by the ARM-

			5 Section 5.4, Secondary Objectives: Clarified that the IES-R will be collected at 'face-to-face' therapy contacts, not all therapy contacts. Section 5.4, Secondary Objectives: Addition of the following: 'Therapeutic alliance will be measured at 3 weeks from start of treatment and at 16 weeks post-randomisation using the ARM-5. The ARM-5 will measure therapeutic alliance and will be administered once during therapy and once after therapy has finished, to check (1) whether the treatment conditions differ in therapeutic alliance and (2) whether there are differential changes in alliance over the course of treatment.' Section 12.1 Assessments: Clarification of time windows for follow-up assessments (+/- two weeks for the 16 week follow-up and +/- one month for the 52 week follow-up). Table 1: Description of Outcome measures: Addition of row for therapeutic alliance ARM-5 measure. Table 2. Schedule of enrolment, interventions and assessments: Addition of row for ARM-5 References: Addition of new reference numbered 52
Minor Amendment 2	4.1	28th August 2018	Section 10.2: Wording amended from: 'If these attempts do not result in contact being made within one month of loss of contact or the planned follow-up, a letter will

			be sent, asking the participant to re-establish contact if they are able to and advising that they will be contacted again at the next follow-up point unless they advise otherwise.' to: 'If these attempts do not result in contact being made within six weeks of loss of contact or the planned follow-up, a letter/email will be sent every month for three further months, asking the participant to re-establish contact if they are able to and advising that they will also be contacted again at the next follow-up point unless they advise otherwise.'
Substantial Amendment 4	5.0	23/11/2018	<u>Section 9.2</u> Addition of the following sentence: Recruitment was originally planned to end in December 2018 but due to delays in opening sites is now planned to end in October 2019. <u>Section 12.0</u>: Voucher amount increased From: Participants will be offered a £10 shopping voucher on completion of the 16 week and 52 week follow-up assessment To: Participants will be offered a £20 shopping voucher on completion of the 16 week and 52 week follow-up assessment <u>Section 15.2</u> Addition of the following sentence: We will also conduct in-depth interviews with key stakeholders (n=4). Using a topic guide, we will explore issues relating to

			commissioning and barriers that may impact on the successful roll-out of a new intervention, looking particularly at contextual factors relevant for different areas and service provisions. <u>Throughout document</u>: Addition of NIHR funding stamp to header.
Substantial Amendment 5	6.0	02/05/2019	<u>Contact Details:</u> Trial Administrator amended from Megan Laird-Phillips to Jade Williams. Email address updated. <u>Section 9.2:</u> <u>Sentence amended from:</u> Recruitment was originally planned to end in December 2018 but due to delays in opening sites is now planned to end in October 2019. <u>To:</u> Recruitment was originally planned to end in December 2018 but due to delays in opening sites, an extension has been made to the study and recruitment is now planned to end in December 2019. <u>Section 14.3</u> <u>Wording amended from:</u> The non-inferiority margin will be 5 points on the 80 point CAPS-5[(1)] scale. To: The non-inferiority margin will be 5 points on the 80 point CAPS-5[(1)] scale, with a common

			standard deviation of 10.3. Wording amended from: This means that if we demonstrate non-inferiority to within 5 points of the gold standard, To: This means that if we demonstrate one-sided non-inferiority to within 5 points of the gold standard, Wording amended from: This results in a final sample size of 192 (inflated from 186) which provides 90% power (nQuery v7.0). To: This results in a final sample size of 192 (inflated from 186) which provides 90% power (nQuery v7.0) with a one-sided 5% significance level. <u>Section 15.1</u> <u>Section changed from:</u> The primary analysis will be performed using analysis of covariance, predicting follow-up CAPS-5 score controlling for baseline CAPS-5 score and important patient characteristics (including all minimisation variables). This will be a complete case intention to treat analysis. Checks will be made to ensure there is no appreciable clustering of outcomes within therapists, but if such clustering exists the primary analysis will be hierarchical. The results will be summarised using point estimates, 95% confidence intervals and p-values. Since this is a non-inferiority design,

			we will be checking whether the confidence interval for the difference between arms lies entirely within the 5 point non-inferiority margin. Participants with missing CAPS-5 score at follow-up will have a CAPS-5 score estimated from available IES-R scores (this will involve building a prediction model using information from participants with both IES-R and CAPS-5 scores). A sensitivity analysis will use multiple imputation to account for missing data if the number of cases lost due to incomplete information exceeds 10%. Secondary outcomes include: CAPS-5, EQ-5D-5L, WSAS, PHQ-9, GAD-7, AUDIT-O, MSPSS, IES-R, ISI, GSES, PTC, adapted CSSRI-EU and CSQ-8. These are all continuous measures and will be analysed similarly to the primary outcome. Transformations will be explored to improve model fit if distributional assumptions are not satisfied. This will be assessed by visual inspection and formal fit statistics compared to decide on the transformation chosen. IES-R scores over time will be explored using a hierarchical modelling (including clustering by therapist if this is identified in the primary analysis) and an appropriate covariance structure allowing for IES-R scores within an individual to be correlated over time. Covariance structures to be explored include autoregressive terms (AR), moving average (MA), and combined terms (ARMA). This will facilitate the fitting of IES-R trajectories over time (since randomisation) interacted with intervention arm, whilst also controlling for the same covariates as the primary analysis. A sensitivity analysis will use multiple imputation to account for missing data if the

			number of cases lost due to incomplete information exceeds 10%. A further sensitivity analysis will account for patient adherence to the protocol using complier adjusted causal effect (CACE) analysis. All analyses will be performed in the R programming language and environment or SPSS. A detailed statistical analysis plan will be signed off before recruitment finishes in line with CTR standard operating procedures (SOPs). <u>To:</u> The primary analysis will be performed using analysis of covariance, modelling 16 weeks follow-up CAPS-5 score controlling for baseline CAPS-5 score, research centre and important patient characteristics: gender, co-morbid depression and time since trauma. Reflecting the sample size calculation, analyses will be undertaken with 2-level hierarchical models with patients clustered within therapists. The primary analysis will utilise multiple imputation with interim collected IES-R scores as auxiliary variables to the imputation. Given that IES-R is likely to be collected 4-5 times for GSH arm patients and 8-12 times for TFCBT-for-PTSD arm patients, there will be bias created by undertaking any multiple imputation model. For this analysis, we will apply a different imputation model to each arm: both containing the relevant number of auxiliary variables (along with baseline CAPS-5 score, research centre, gender, age and time since trauma and clustered by therapist). Imputed datasets will then be combined before undertaking analyses. The results will be summarised using point estimates, and 1-sided 95% confidence

			intervals and p-values (in line with the sample size calculation). Since this is a non-inferiority design, we will be checking whether the confidence interval for the difference between arms lies entirely within the 5 point non-inferiority margin. Where the treatment effect and 1-sided 95% confidence interval is entirely greater than 0 then superiority will be assessed with a 2-sided 90% confidence interval and relevant p-value. For the primary outcome, the complete case intention to treat analysis and per-protocol analysis are both of scientific interest and will be reported as sensitivity analyses under a non-inferiority framework. A further sensitivity analysis of the primary outcome under a non-inferiority framework will implement a different multiple imputation model: IES-R scores taken from 5 clinic visits for the TFCBT-for-PTSD arm patients that align similarly in time to those of the GSH arm patients will be used as auxiliary variables in an imputation model (this one with both arms combined) (along with baseline CAPS-5 score, research centre, gender, age and time since trauma and clustered by therapist. A further sensitivity analysis of the primary outcome under a non-inferiority framework will account for patient adherence to the protocol using complier adjusted causal effect (CACE) analysis. Secondary outcomes include: CAPS-5 at 52 weeks follow-up, EQ-5D-5L, WSAS, PHQ-9, GAD-7, AUDIT-O, MSPSS, IES-R, ISI, GSES, PTC, adapted CSSRI-EU and CSQ-8. These are all continuous measures and will be analysed using multiple imputation to account for

			missing data under a non-inferiority framework. Transformations will be explored to improve model fit if distributional assumptions are not satisfied. This will be assessed by visual inspection and formal fit statistics compared to decide on the transformation chosen. In the cases of all multiple imputation models, we will explore whether the baseline version of the outcome, research centre, gender, co-morbid depression and time since trauma are associated with the missingness of the outcome. Multiple imputation will always be undertaken but we will note where these explorations suggest that the mechanism is missing not at random.IES-R scores over time will be explored using a hierarchical modelling (including clustering by therapist if this is identified in the primary analysis) and an appropriate covariance structure allowing for IES-R scores within an individual to be correlated over time. This will facilitate the fitting of IES-R trajectories over time (since randomisation) interacted with intervention arm, whilst also controlling for the same covariates as the primary analysis. Note that these are likely collected 4-5 times for GSH arm patients and 8-12 times for TFCBT-for-PTSD arm patients. All analyses will be performed in the stata programming language and environment, with REALCOM software used for multi-level multiple imputation and SPSS for initial storage and data manipulation. A detailed statistical analysis plan will be agreed and signed off (by trial statistician, chief investigator, CTR MBN Director and co-applicant statistician) before final primary

			analysis data collection finishes, in line with CTR standard operating procedures (SOPs). Section 15.2 Sentence amended from: We will also conduct in-depth interviews with key stakeholders (n=4). To: We will also conduct in-depth interviews with up to ten key stakeholders. Section 15.4 Addition of the following paragraph: A therapist training & support sub-study will explore whether therapist-rated service support for TFCBT affects the quality of TFCBT sessions delivered in clinical practice. RAPID therapists will be asked to complete a questionnaire, and in conjunction with the TFCBT session fidelity assessments, the data generated will be analysed in order to explore factors extraneous to the research study (including individual training and, service support for CBT) which may influence the quality of CBT sessions delivered in routine clinical practice. Therapists will be offered a £10 voucher to thank them for their participation. References Addition of the following references: (61) Committee for Proprietary Medicinal Products. Points to consider on switching between superiority and non-inferiority. British Journal of Clinical Pharmacology. 2001;52(3):223-8.

			(62) Rehal S, Morris TP, Fielding K, Carpenter JR, Phillips PPJ. Non-inferiority trials: are they inferior? A systematic review of reporting in major medical journals. BMJ Open. 2016;6(10):e012594

2 Synopsis

Acronym	RAPID
Internal ref. no.	319
Clinical phase	III
Funder and ref.	HTA 14/192/97
Trial design	Randomised controlled non-inferiority trial, with nested process evaluation to assess fidelity, adherence and factors that influence outcome.
Trial participants	Adults with Post-Traumatic Stress Disorder (PTSD) to a single traumatic event
Planned sample size	192
Inclusion criteria	Aged 18 or over Screen positive for PTSD on the Traumatic Screening Questionnaire (TSQ) following a single traumatic event experienced at any age Regular access to the internet in order to complete the modules and homework required by the Guided Self Help (GSH) programme Provide informed consent After a two week monitoring period, continue to meet Clinician Administered PTSD Scale (CAPS-5) criteria for mild to moderate PTSD (less than 50 on the CAPS-5) PTSD is the primary diagnosis
Exclusion criteria	Inability to read and write fluently in English Previous completion of a course of trauma-focused psychological therapy for PTSD

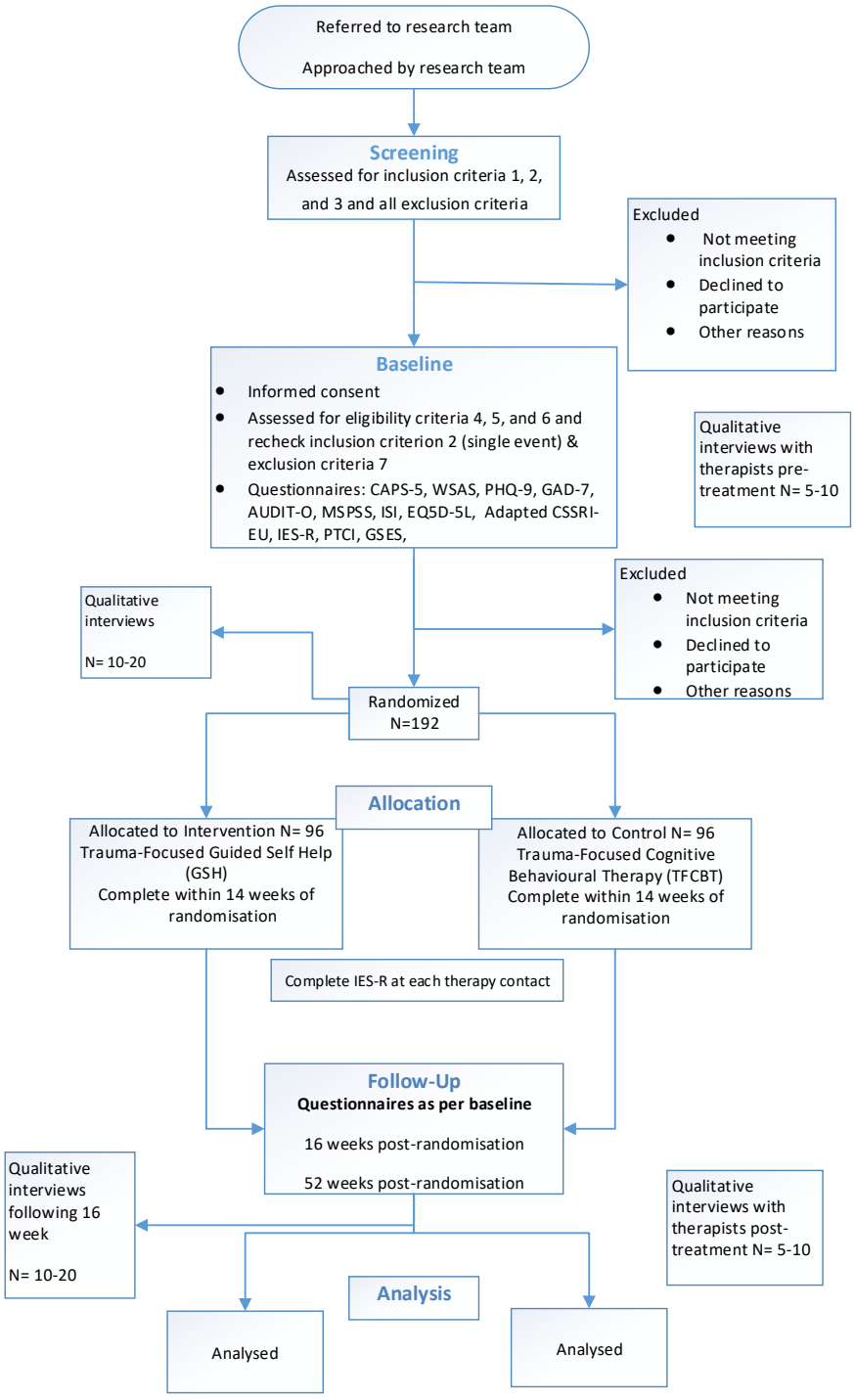
	Currently engaged in a psychological therapy Change in psychotropic medication in last four weeks Current psychosis Substance dependence Active suicide risk
Treatment duration	8-12 weeks
Follow-up duration	52 weeks post-randomisation
Planned trial period	36 months
Primary objective	To determine whether, for patients with Post-Traumatic Stress Disorder (PTSD), an internet TFCBT based focused Guided Self Help (GSH) programme is not inferior to individual Trauma-focused Cognitive Behavioural Therapy (TFCBT), as judged by reduced symptoms of PTSD at 16 weeks post-randomisation.
Secondary objectives	To determine whether, for patients with PTSD, an internet TFCBT based GSH programme is not inferior to individual TFCBT, as judged by reduced symptoms of PTSD at 52 weeks post-randomisation. To determine whether, for patients with PTSD, an internet TFCBT based GSH programme is not inferior to individual TFCBT, as judged by improved quality of life at 16 weeks and 52 weeks post-randomisation. To determine, for patients with PTSD, the impact of an internet TFCBT based GSH programme on functioning, symptoms of depression, symptoms of anxiety, symptoms of PTSD, alcohol use, perceived social support, insomnia, self-efficacy and cognitions at 16 weeks and 52 weeks post-randomisation.

	To determine whether, for patients with PTSD, an internet TFCBT based GSH programme is cost-effective relative to individual TFCBT at 16 weeks and 52 weeks post-randomisation. To determine what factors may impact effectiveness and successful roll-out of internet TFCBT based GSH for PTSD in the NHS, if the GSH programme is shown to be effective.
Primary outcomes	PTSD symptoms as measured by CAPS-5 at 16 weeks post-randomisation
Secondary outcomes	PTSD symptoms as measured by CAPS-5 at 52 weeks post-randomisation Measured at 3 weeks from start of treatment and 16 weeks post randomisation: Therapeutic alliance as measured by the ARM-5 Measured at 16 weeks and 52 weeks post-randomisation: PTSD symptoms as measured by IES-R (also measured at each therapy session) Quality of life as measured by EQ-5D-5L Functional impairment as measured by WSAS Depression as measured by PHQ-9 Anxiety symptoms as measured by GAD-7 Alcohol use as measured by AUDIT-O Social Support as measured by MSPSS Insomnia as measured by ISI Self-efficacy as measured by GSES

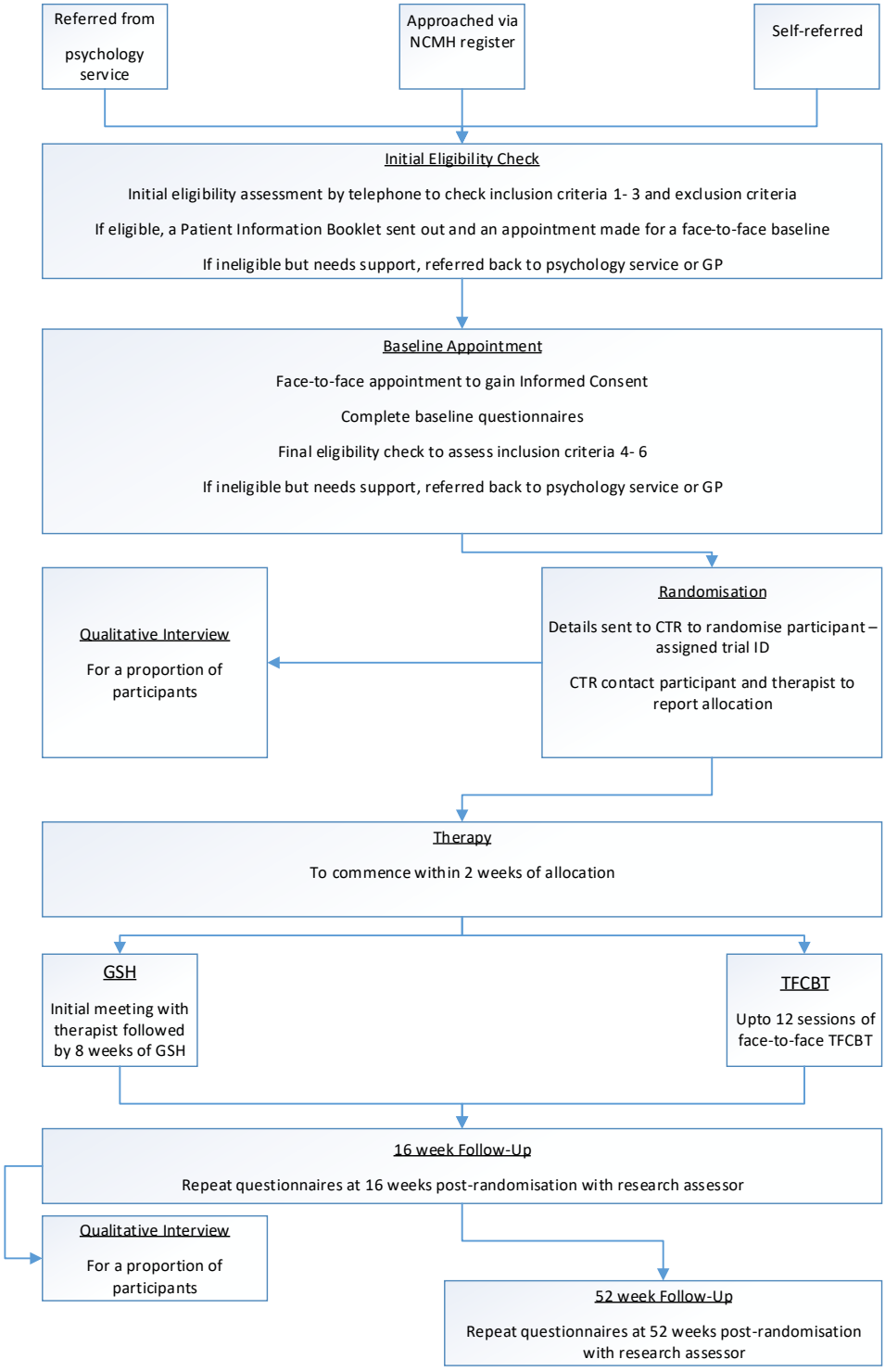
	Cognitions as measured by PTCI Health care costs as measured by adapted CSSRI-EU Additional measure at 16 weeks post-randomisation: Client Satisfaction Questionnaire (CSQ-8)
Intervention	Spring (Internet Guided Self Help Programme based on TFCBT) Individual face-to-face TFCBT

3. Trial summary & schema

3.1 Trial schema



3.2 Participant flow diagram



3.3 Trial lay summary

The aim of this research is to determine if trauma-focused guided self help (GSH) using a web-based programme provides a faster and cheaper treatment for Post-Traumatic Stress Disorder (PTSD) than individual trauma-focused cognitive behavioural therapy (TFCBT), whilst being equally effective.

PTSD is a common, often disabling mental disorder that can occur following major traumatic events such as abuse, assaults and accidents. Typical symptoms include: distressing reliving in the form of nightmares or intrusive thoughts; avoidance of reminders; distorted thoughts such as feeling shame for being abused; and hyperarousal, for example through increased irritability and jumpiness. Recent news stories highlight the devastating impact that PTSD can have (e.g. the Savile Effect) and how the absence of timely intervention can lead to long-term suffering. They have also increased public awareness of PTSD and, potentially, the likelihood of presentation for help.

The first choice treatments for PTSD are individual talking treatments (including TFCBT) of 12-16 hours duration. Unfortunately, the limited number of therapists available and length of treatment means that there are long NHS waiting lists of up to 18 months. PTSD sufferers may also have difficulty committing to weekly appointments, especially if they are working, have childcare commitments or are scared to go out alone or to new places. If equally effective treatments could be developed that take less time and can be largely undertaken in a flexible manner at home, this would improve accessibility, reduce waiting times and hence the burden of disease. GSH has the potential to address this gap.

The proposed research is a randomised controlled trial of carefully developed GSH using a web and app-based programme, with up to three hours contact with a therapist either in person, via internet video link or telephone, versus face-to-face TFCBT. Outcomes will include measures of PTSD, depression, anxiety, insomnia, self-efficacy, thoughts, quality of life and disability. Information will be collected to estimate the costs of delivering the GSH and of the savings if it is successful from the perspective of the patient, their family, the health service and society as a whole. A sample of therapists and participants will be interviewed in more detail to explore the factors that influence acceptability, including what helps and hinders uptake, ability to complete the intervention and other factors associated with outcome. Interviewees will be encouraged to reflect, and provide accounts of their own experiences in their own words, allowing them to initiate and develop the topics that are important to them, while keeping the talk relevant to the research.

Two of the research team are former PTSD sufferers, one has been involved as a key member of the research team from the start. There will be an independent PPI member of the steering group and a PPI advisory group to advise on all aspects of the study.

Promotion of the trial will occur throughout the study through study webpages, social media, local and national media. The results will be presented to the participants through an end of study report and published in high quality, open access journals.

4 Background

Post-Traumatic Stress Disorder (PTSD) is a common mental disorder that may develop following exposure to exceptionally threatening or horrifying events. Characteristic symptoms include persistent intrusive recollections, avoidance of trauma-related stimuli, emotional numbing and hyper-arousal.[2, 3] About 3% of the adult population suffer from current PTSD[4] and average symptom duration is normally prolonged in those who are untreated.[5] PTSD is associated with substantial co-morbidity[5-9] and significant economic burden.[10, 11]

A number of psychological approaches have been developed to treat PTSD. Evidence suggests that the most effective approaches are those that are based on trauma focused cognitive behavioural therapy (TFCBT) (including trauma focused cognitive therapy) and eye movement desensitization and reprocessing (EMDR).[12] TFCBT typically involves some degree of structured exposure to and processing of unwanted traumatic memories and avoided stimuli, alongside cognitive restructuring of dysfunctional beliefs. EMDR is a psychological therapy that involves exposure to unwanted and distressing memories whilst focusing on bilateral stimuli. TFCBT and EMDR have become the treatments of choice for PTSD, recommended by clinical guidelines in the UK and internationally.[13-15] TFCBT models differ slightly in the number of treatment sessions that are recommended. NICE recommended treatment of 8-12 sessions lasting 60-90 minutes for individuals who had experienced a single trauma, with a recommendation of more than 12 sessions in more chronic and complex cases.

Despite a growing consensus that trauma focused psychological therapies (TFPTs) represent the most effective way of treating PTSD, there remains a shortage of suitably qualified therapists able to deliver these interventions in many places and lengthy waiting times are common. If left untreated, PTSD is associated with functional and emotional impairment, reduced quality of life, a predisposition for the development of other psychiatric and physical illnesses, increased suicidal ideation, higher healthcare utilisation, and higher rates of alcohol abuse and dependence[16-22] Current treatment also requires a considerable commitment from the service user to attend appointments on a regular basis over several months. Treatment can be difficult for some people to access, due to factors such as perceived stigma about attending mental health services, difficulty getting time off work to attend appointments, problems accessing or arranging suitable childcare and travel for people living in remote areas.[23-25] As a result of these and other factors drop-out from treatment can be high.[12]

Guided Self Help (GSH) combines the use of self help materials (e.g., a work-book, or a website), with regular guidance from a trained professional and requires less therapist time than an equivalent therapist-administered treatment. If effective, GSH would offer a time-efficient and accessible treatment option with the potential to reduce waiting times and intervention costs, and lessen the burden of PTSD to the NHS and society. There is good evidence of the efficacy of GSH in other mental health disorders.[26] In recognition of these findings NICE recommended that an RCT of GSH

should be conducted to assess the efficacy and cost-effectiveness of guided self help compared with trauma focused psychological interventions for mild and moderate PTSD12.

The study team has systematically developed a novel, internet-based GSH programme for PTSD based on TFCBT. This was developed over a number of years following MRC guidance for the development of a complex intervention,[27]with significant input from PTSD sufferers and professional stakeholders. The Phase I work was completed between 2007 and 2010. A modelling phase included key stakeholders in focus groups and semi-structured interviews to inform the content, delivery and guidance of a GSH programme for PTSD. Data was analysed using qualitative methodology and used to inform the first prototype. The prototype was piloted twice with a total of 19 participants with PTSD and refined on the basis of qualitative and quantitative results. Quantitative results strongly supported the potential of the programme to effectively treat PTSD.[28]

An interactive online version of the programme was produced through a Knowledge Transfer Partnership (KTP) between Health Care Learning Limited Ltd (HCL) and Cardiff University. The partnership combined HCL's expertise in developing high quality internet-based programmes, with the academic team's experience of developing and evaluating psychological interventions for PTSD. A Phase II RCT of the intervention was completed between 2012 and 2014. Forty-two participants with mild to moderate PTSD after a single traumatic event were randomised to receive immediate GSH or delayed treatment.

PTSD sufferers' symptoms improved by over 50% (completers only) and over 40% (intention to treat) with an average of 149 minutes of therapist input; effect sizes that compare favourably with those found for therapist-delivered TFPT. The treatment group had significantly lower levels of traumatic stress symptoms, depression, anxiety and functional impairment at post-treatment and one month follow-up, in comparison to the delayed treatment group, who improved to the same degree after receiving GSH for PTSD. Results of the Phase I and Phase II work indicate a strong rationale for conducting a Phase III RCT to determine whether GSH represents a treatment option that should be routinely used in the care of PTSD sufferers, as it is for depression and numerous anxiety disorders.

A Cochrane review of RCTs of online SH for PTSD in comparison to face-to-face therapy, waitlist/ usual care[29] found two other previous studies.[30, 31] The first compared online SH with 104 minutes of guidance to a waitlist in 42 adults with PTSD.[30] A large within group effect size was found in the GSH group from pre to post-treatment for self-reported PTSD symptoms (Cohen's d = 1.18) but a smaller between groups effect size was found post-treatment, due to symptom improvement in the control group. The second RCT compared online GSH to a delayed treatment minimal attention group in 62 PTSD sufferers.[31] A larger between group effect size of d = 1.25 was found. The interventions included in both studies were largely text-based and may not have been optimal in terms of usability.

There have been no comparative trials of online GSH and face-to-face therapy to date, precluding firm decisions being made on whether to deliver GSH for PTSD in the NHS. The proposed study will

address this by generating high quality scientific evidence for an intervention already developed by us through state of the art methodology. We will test online GSH as a treatment for adults who have been exposed to a single traumatic event. We will investigate whether it is as effective as TFCBT and also whether there are any negative consequences of the intervention. A potential risk is an increase in psychological distress due to exposure to the trauma. However, the pilot study did not find any harms from the GSH intervention and we do not expect any in this study.

4.1 Rationale for current trial/Justification of Treatment Options

We are conducting this RCT to determine whether online GSH is a suitable alternative to face-to-face therapy for people with PTSD exposed to a single traumatic event with the aim of increasing access to, and ease of, treatment. We will also examine whether GSH represents a cost saving to the NHS. Pilot trials of the GSH programme have shown promise and a definitive trial is now needed. We will compare the new GSH with standard care, currently TFCBT.

5 Trial objectives/endpoints and outcome measures

The aim of the research is to determine whether internet delivered GSH based on TFCBT is non-inferior and cost-effective compared to individual face-to-face TFCBT for PTSD in the NHS in the United Kingdom. Secondary aims are to describe the experience of receiving the GSH from the patients' perspective, and the delivery of the GSH from the therapists' perspective.

5.1 Primary objectives

The primary objective of the trial is to determine:

Whether an online TFCBT based GSH programme is not inferior to individual TFCBT for patients with PTSD as judged by reduced symptoms of PTSD at 16 weeks post-randomisation.

5.2 Secondary objectives

The secondary objectives of the trial are to determine:

1. Whether an online TFCBT based GSH programme is not inferior to individual TFCBT for patients with PTSD as judged by reduced symptoms of PTSD at 52 weeks post-randomisation.
2. Whether an online TFCBT based GSH programme is not inferior in effectiveness to individual TFCBT for patients with PTSD as judged by improved quality of life at 16 weeks and 52 weeks post-randomisation.
3. The impact of an online TFCBT based GSH programme on functioning, symptoms of depression, symptoms of anxiety, symptoms of PTSD, alcohol use, insomnia, perceived social

support, self-efficacy and cognitions for people with PTSD at 16 weeks and 52 weeks post-randomisation.

4. Whether an online TFCBT based GSH programme is cost-effective relative to individual TFCBT for patients with PTSD at 16 weeks and 52 weeks post-randomisation.

5. The factors which may impact effectiveness and successful roll-out of online GSH for PTSD in the NHS if the GSH programme is shown to be effective.

5.3 Primary outcomes measure(s)

Our primary outcome will be symptoms of PTSD over the previous week measured by the Clinician Administered PTSD Scale for DSM5 (CAPS-5)[1] at 16 weeks post-randomisation. The CAPS-5 is a 29 item structured interview for assessing PTSD diagnostic status and symptom severity. The CAPS-5 is the gold standard in PTSD assessment and can be used to make a current (past month) or lifetime diagnosis of PTSD or to assess symptoms over the past week. Items correspond to the DSM5 criteria for PTSD. Previous versions of the CAPS-5 have excellent reliability and excellent convergent and discriminant validity, diagnostic utility, and sensitivity to clinical change. [1]

5.4 Secondary outcomes measure(s)

Secondary outcome measures (see Table 1. Below) will be collected at 16 weeks post-randomisation to assess the effect of the intervention, and the majority of these measures will be collected again at 52 weeks post-randomisation to determine whether any improvements are sustained. We will include self-report measures that are routinely collected by IAPT services at present (Impact of Event Scale – revised[32] for traumatic stress; Work and Social Adjustment Scale[33] for quality of life/functional impairment; Patient Health Questionnaire-9[34] (PHQ-9) for depression; General Anxiety Disorder-7[35] (GAD-7) for anxiety; and AUDIT-O[36] for alcohol use). In addition, the Multidimensional Scale for Perceived Social Support[37] will be used to assess perceived social support and an amended version of the amended Client Socio Demographic and Service Receipt Inventory European Version (CSSRI-EU)[38] questionnaire will be used to determine the level of healthcare resource utilisation for health economic analysis. Changes in health related quality of life will be measured by the EQ-5D-5L[39] and changes in sleep will be measured by the Insomnia Severity Index (ISI)[40]. The Post-Traumatic Cognitions Inventory [41] and General Self Efficacy Scale (GSES[42, 43]) will be collected to determine effects on cognitions and self-efficacy. In addition to being collected as a secondary outcome measure, the IES-R will be collected at each face-to-face therapy contact by the therapist to provide clinical feedback and also to facilitate imputation for missing data, if required. How frequently it is collected will depend on the frequency of therapist contact, but is likely to be weekly in the TFCBT arm and fortnightly in the GSH arm. The Client Satisfaction Questionnaire (CSQ-8)[44] will be collected at 16 weeks post-randomisation to evaluate treatment satisfaction. Therapeutic alliance will be measured at 3 weeks from start of treatment and at 16 weeks post-randomisation using the ARM-5. The ARM-5 will measure therapeutic alliance and will be administered once during therapy and once after therapy has finished, to check (1) whether the treatment conditions differ in therapeutic alliance and (2) whether there are differential changes in alliance over the course of treatment.

Table 1. Description of outcome measures

Outcome	Secondary Time Points	Measure	Explanation of Measure
PTSD symptoms	16 weeks /52 weeks	CAPS-5	As above
PTSD Symptoms	16 weeks/52 weeks and at therapy sessions	IES-R	The Impact of Event Scale – Revised (IES-R) is a brief PTSD self-report measure and has been used in many international studies[45]. The IES-R is the outcome measure of choice for evaluating improvement in PTSD symptoms in IAPT services in England.
Functional Impairment	16 weeks/52 weeks	WSAS	The Work and Social Adjustment Scale (WSAS) is a self-report measure, which assesses the impact of a person's mental health difficulties on their ability to function in terms of work, home management, social leisure, private leisure and personal or family relationships. The WSAS is the outcome measure of choice for evaluating improvement in functioning in IAPT services. The WSAS has been demonstrated to show good reliability and validity and is sensitive to change.[33]
Depression Symptoms	16 weeks/52 weeks	PHQ-9	The Patient Health Questionnaire (PHQ-9) is a widely used reliable and well-validated brief self-report measure of depression.[34] It is the outcome measure of choice for evaluating improvement in depressive symptoms in IAPT services.[46]
Anxiety Symptoms	16 weeks/52 weeks	GAD-7	The General Anxiety Disorder (GAD-7) is a widely used reliable and well-validated brief self-report measure of anxiety. It is the outcome measure of choice for evaluating improvement in anxiety symptoms in IAPT services. [46]
Alcohol symptoms	16 weeks/52 weeks	AUDIT-O	The Alcohol Use Disorders Test (AUDIT-O[46] contains 10 multiple choice questions on quantity and frequency of alcohol consumption, drinking behaviour and alcohol-related problems or reactions over the preceding 3 months.

Social Support	16 weeks/52 weeks	MSPSS	The Multidimensional Scale for Perceived Social Support (MSPSS) is a widely used 12-item Likert scale measuring the subjective assessment of adequacy of social support from family, friends, and partners.[47] The reliability, validity, and factor structure of the MSPSS have been demonstrated with a number of populations.[37],[47],[48]
Quality of Life	16 weeks/52 weeks	EQ-5D-5L	The EQ-5D-5L[39] is a widely used instrument in health economic analysis and recognised by NICE as an appropriate measure for health related quality of life. The questionnaire provides a simple descriptive profile, which translates to a single utility score for health status. The first part of the instrument identifies the extent of perceived problems – across five levels - in each of five life dimensions: mobility; self-care; usual activities; pain and discomfort; and anxiety and depression. The responses to each of the five questions are used to generate a utility score for self-rated health status on a 0-1 scale, where 0 represents the worst possible health state and 1 the best possible health state. The second part is a visual analogue scale, which allows the responder to indicate their current health status on a 0-100 scale. The utility score (ranging from 0-1) will be used to estimate the extent of QALY gains arising from the intervention over time.
Service Costs	16 weeks/52 weeks	Adapted CSSRI-EU	The Client Socio Demographic and Service Receipt Inventory European Version (CSSRI-EU) questionnaire[38] is a semi-structured questionnaire, developed from the original version – Client Service Receipt Inventory, which has been widely used since its development in the 1980s - to embrace wider contexts and an international perspective. The CSSRI collects information necessary to individually estimate the detailed care service costs incurred by users affected by mental disorders, through specific information about dwelling conditions, life situation, received incomes and benefits, utilisation of health services including medication, social assistance, procedures and other communal services during a

			retrospective period of time (during the last month, last 3 months, and last 6 months). The data collection allows for the identification of a basic package of care. The costs per unit for every received service, developed procedure, and medication consumed will be calculated a posteriori, and later used to calculate the total cost of all interventions. The CSSRI-EU provides a standardised yet adaptable method for collating service receipt and associated data alongside assessment of patient outcomes.[49]
Sleep	16 weeks/52 weeks	ISI	The Insomnia Severity Index (ISI) is a widely used 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. It has been shown to be reliable and valid in terms of detecting insomnia and in measuring treatment response in clinical patients.[40]
Cognitions	16 weeks/52 weeks	PTCI	The Post-Traumatic Cognitions Inventory (PTCI) was developed as a 33-item scale, which is rated on a Likert scale ranging from 1 (totally disagree) to 7 (totally agree); a shortened form has also been developed [41] Scale scores are formed for three subscales: Negative cognitions about self, Negative cognitions about the world and self-blame. The PTCI shows good internal consistency, high test-retest reliability and good convergent validity with other measures of trauma related cognitions. The PTCI also shows promise in being able to differentiate individuals with and without PTSD.
Self-efficacy	16 weeks/52 weeks	GSES	The General Self-Efficacy Scale (GSES) is a 10-item, four point Likert scale that is used to measure self-efficacy. It has been used in more than 1,000 studies, is reliable and well-validated [42], [50]
Treatment satisfaction	16 weeks	CSQ-8	The Client Satisfaction Questionnaire (CSQ-8) is a widely used 8-item, Likert Scale which was developed through literature review and expert ranking, pretested on 248 mental health clients in five settings.[44] It is a self-report statement of satisfaction with a high degree of internal consistency, good concurrent validity

			and reliability[51] and is brief and easy to complete.
Therapeutic Alliance	3 weeks into treatment / 16 weeks	ARM-5	The ARM-5 is a validated short 5 item version of the 28-item Agnew Relationship Measure, comprising client and therapist versions containing parallel items [52].

6 Trial design and setting

The design is that of a phase III pragmatic randomised controlled non-inferiority trial with assessors masked to treatment allocation. Individual randomisation will be used. The trial will contain a nested process evaluation to assess fidelity to treatment delivery, adherence to treatment and factors that influence outcome. Quantitative and qualitative research methods will be used.

Primary and secondary NHS care psychological treatment settings will be included covering urban and rural, economically and non-economically deprived areas of the UK in Coventry, Greater Manchester, London, Luton, South Wales, South West Yorkshire and Warwick. We aim to recruit 192 participants with mild to moderate PTSD following a single traumatic event. Follow ups will take place at 16 weeks and 52 weeks and the end of the trial will be defined as 'last participant, last data collection'.

Participants will be individually randomised to either the intervention group or control group. The intervention will consist of internet based Guided Self Help based on TFCBT. The control group will be usual care, that is, face-to-face individual TFCBT.

Baseline and follow up data will be questionnaires collected by a research assistant or research network personnel, where possible, using electronic data capture. Appointments will be conducted either in the clinic, in the participant's home or in another place convenient for the participant. Follow ups may be completed by telephone if that suits the participant.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. We do not expect the risks to be higher than for standard care (which for many patients in the NHS will be a waiting list for TFCBT). A copy of the trial risk assessment may be requested from the Trial Manager and will be tabled periodically at the TMG. The trial risk assessment is used to determine the intensity and focus of monitoring activity.

7 Site and Investigator selection

This trial will be carried out at participating sites within the UK. We will have 4 research centres based in Cardiff, Manchester, London and Edinburgh. Within each centre up to four sites will be recruited. All sites who are interested in participating in the trial will be required to complete an assessment form to confirm that they have adequate resources and experience to conduct the trial.

Before any Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the RAPID trial email account:

- Favourable opinion from Main Ethics committee

- The approval letter from the site's R&D Department, following submission of the Site Specific Information (SSI) form
- A signed Trial Agreement (PI and sponsor signature)
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all site personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) with local logos
- A copy of the most recent approved GP letter

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial pack holding all the documents required to recruit into the trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by a meeting at the individual site or by teleconference if attendance of key personnel at site is unfeasible.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration.

8.1 Inclusion criteria

Wide eligibility criteria will be used to ensure good external validity. Given the high rate of co-morbidity of PTSD and other conditions such as depression and substance misuse, individuals with co-morbidity will be included if they satisfy the other inclusion/exclusion criteria and PTSD is considered the primary diagnosis. This is consistent with NICE guidance for the treatment of PTSD[13] and will result in a pragmatic trial.

1. Aged 18 or over
2. Screen positive for PTSD (using Trauma Screening Questionnaire) to a single traumatic event experienced at any age.

3. Have regular access to the internet in order to complete the steps and homework required by the GSH programme
4. Willing and able to give informed consent to take part
5. After a two week monitoring period, continue to meet CAPS5 criteria for mild to moderate PTSD (less than 50 on the CAPS5)
6. PTSD is the primary diagnosis

Trained researchers will assess criteria 1, 2 and 3 at a telephone screening interview and criteria 4, 5 and 6 at a face-to-face baseline interview 2 weeks later. Criterion 2 (single event) will also be re-checked at the baseline interview.

With reference to criterion 2, previous work with more complex and severe forms of PTSD, e.g. following prolonged and repeated trauma suggests that it often requires increased therapist time and is therefore less likely to be effectively treated by GSH. In terms of criterion 5, symptoms can remit when monitored, hence the 2 week monitoring period.

8.2 Exclusion criteria

The person may not enter the trial if ANY of the following apply:

1. Inability to read and write fluently in English
2. Previous completion of a course of trauma-focused psychological therapy for PTSD
3. Currently engaged in a psychological therapy
4. Change in psychotropic medication in the last four weeks
5. Current psychosis
6. Substance dependence
7. Active suicide risk

All criteria will be assessed at the telephone screening interview. If the person meets criteria 3 or 4, they will be deemed temporarily ineligible and the researcher will arrange to contact them again in a 4-8 weeks' time to see if they become eligible. Criterion 7 will also be re-checked at the baseline interview.

9 Recruitment, Screening and registration

9.1 Participant identification

Prospective participants will be identified through Primary Care Mental Health Services (PCMHS) in South Wales and through Improving Access to Psychological Therapy (IAPT) services in England. Three centres in Cardiff, Manchester and London will initially oversee recruitment at up to 3 sites each. More sites may be added if necessary. Primary care workers in these services will be educated

about the study and the eligibility criteria, and asked to identify and refer patients who may be experiencing PTSD and meet eligibility criteria 1 & 3 (aged 18+ with regular access to the internet). A small amount of merchandise (such as pens, post-its and mugs) will be used to remind referrers of the study. They will be provided with a Summary Information sheet of the study, which they can discuss with the patient. With the patient's consent, they will pass their contact details to the researchers by secure fax or a telephone call. The researcher will then telephone the patient to confirm they meet the first three eligibility criteria and do not appear to meet any exclusion criteria. Criterion 2 will be assessed using the Trauma Screening Questionnaire. If the patient is eligible, the researcher will send them a copy of the Participant Information Booklet to read before the appointment. If the patient is found to be ineligible, they will be referred back to the psychology service.

The Cardiff centre will also recruit participants through the National Centre for Mental Health (NCMH) cohort of participant volunteers. The cohort of over 6500 participants (increasing by around 150 per month) with lived experience of a mental illness currently includes 725 individuals with a diagnosis of PTSD, the majority of whom live in South Wales. A member of the NCMH team will contact potentially eligible individuals who have consented to being contacted about future research, to screen for eligibility and invite participation if eligible.

In addition to the methods described above, individuals referred to the local tertiary traumatic stress services will be screened by service clinicians and details of potentially eligible patients passed to the research team as described above. Information about the study will be communicated across all primary and secondary care services (including counselling services) in the recruitment areas and University Student Support Services (these were a source of recruitment in the Phase II study). A limited number of leaflets will be available at key NHS services such as IAPT services, GP surgeries, Accident and Emergency services and out-patient clinics. We will publicise the trial publicly in conjunction with the NCMH communications team. This will include targeted press releases to local media with the offer of an interview with one of the study team, news items and advertisements on the NCMH website (www.ncmh.info), and a social media campaign to raise awareness of the study. We will seek to explore opportunities to recruit through the Criminal Justice System by linking with Victim Support, Sexual Assault Referral Centres (SARCs) and HM Court Services.

A screening log of all ineligible and eligible but not consented/not approached will be kept at each site so that any biases from differential recruitment will be detected. The screening log should be sent to the RAPID email address every month and should not contain patient identifiable information. For those participants referred from a clinical service who are not eligible to take part or who decline to give consent to the trial will be referred back to that service. Those who self referred to the trial will be advised to contact their GP if they would like to seek treatment or discuss their symptoms.

9.2 Recruitment rates

A total of 192 participants will be recruited with an average expected rate of just over 3 per co-ordinating centre per month.
Recruitment was originally planned to end in December 2018 but due to delays in opening sites an extension has been made to the study and recruitment is now planned to end in December 2019.

9.3 Informed consent

The potential participant will receive the Patient Information Booklet at least 24 hours before the baseline assessment. The researcher will conduct the first screening assessment via telephone to confirm inclusion criteria 1- 3 and all the exclusion criteria. Eligible participants will be asked to complete a daily diary for two weeks to monitor their symptoms and the researcher will make a baseline appointment for 2-4 weeks time. It has been found that some individuals experience a significant reduction in symptoms following diary completion, hence the inclusion of the monitoring period, but this data will not be used for research purposes.

The baseline appointment will be conducted face-to-face and will begin with gaining consent. Consent may be taken by any researcher trained in GCP and the trial specific consent process. The consent process will begin by the researcher reading through the Patient Information Booklet with the patient and giving them to time to ask questions about the study. They will check:

1. Whether the participant has any queries arising from the information booklet, and will answer any that do arise.
2. That the participant understands their participation is voluntary and that they are free to withdraw at any time without giving any reason, without their medical care or legal rights being affected. They understand that data already collected may be used for research purposes unless they ask otherwise.
3. They understand that data collected during the study may be looked at by individuals from the study team, from the NHS Trust or from regulatory authorities.
4. They are aware that they may be contacted by text, telephone, e-mail or letter where this is necessary for the conduct of the study, and they may be offered an interview.
5. They understand that the GP will be informed of their participation in the study.
6. They understand that the therapy sessions and interviews are to be audio recorded.
7. Whether they agree to being approached with information inviting them to take part in future research.
8. They understand that information collected may be used to support other research in the future, and may be shared anonymously with other researchers.
9. Whether they agree for their details to be added to the National Centre for Mental Health PTSD cohort.
10. Whether the participant agrees to take part in the study.

The member of the research team who is conducting the assessment will then request the participant to complete the triplicate study Consent Form. One copy should be given to the participant, the original copy should be kept in the investigator site file and a further copy should be posted to the RAPID team at the CTR.

All work will be conducted in full compliance with the Data Protection Act.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

9.4 Registration and Randomisation

9.4.1 Registration

At the baseline assessment, following the consent process, the researcher will administer the CAPS-5 to assess inclusion criterion 5, as well as assessing criteria 4, 6 and re-checking the PTSD symptoms are to a single event (criterion 2). They will also re-check that the person is not actively suicidal (exclusion criterion 7). Once consent has been provided and eligibility confirmed, participants will be individually randomised to receive either GSH or TFCBT.

9.4.2 Randomisation

Individual randomisation will be performed by CTR and will be conducted using a minimisation algorithm developed by CTR in accordance with CTR SOPs. This will ensure balance between trial arms on gender but will retain a random element and will be stratified by research centre. Allocations will be communicated to the local PIs/therapists. A randomisation protocol will be written and signed off before recruitment begins in line with CTR policy. Outcome assessors will be blinded to treatment allocation as far as possible. Participants will be asked not to reveal the intervention they received to assessors at follow-up interviews.

Please note, only when written informed consent has been obtained from the participant and they have been randomised/enrolled into the trial can they be considered a trial participant.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants' care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal from the trial intervention
2. Withdrawal from follow-up interviews/questionnaires
3. Withdrawal from both the trial intervention and follow-up interviews/questionnaires
4. Withdrawal as for point 3, plus withdrawal to use previously collected data. Unless specifically stated otherwise however, consent to use existing data will be assumed.

In circumstances 1-3, the withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. In circumstance 4, any trial data collected for this participant must be deleted.

A participant may withdraw or be withdrawn from the intervention for the following reasons:

- Withdrawal of consent to participate in the intervention by the participant
- Any alteration in the participant's condition which justifies the discontinuation of the intervention in the Investigator's opinion. For example, developing a condition which would exclude them from the study based on the eligibility criteria.

In the case of suicidal ideation, the therapist should assess the participant to determine whether or not they can continue or need to be referred elsewhere. In the case that a participant scores 50+ on the CAPS-5 at follow-up, they will also need to be assessed by the clinical team and may be offered additional treatment. Participants who solely withdraw/are withdrawn from the intervention will continue in follow up unless they withdraw their consent for this.

In all instances participants who consent and subsequently withdraw should complete a withdrawal form or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. This withdrawal form should be faxed to the Trial Manager. Any queries relating to potential withdrawal of a participant should be forwarded to the RAPID email account.

10.2 Loss to follow up

Unless a participant has withdrawn consent to participation, repeated attempts using different approaches will be made to contact participants who cannot be easily contacted. In a step-wise manner, this will involve checking contact details with their study therapist, calling the individual on

all contact numbers provided on various days of the week and at different times, sending e-mails and a letter to the addresses provided. If contact can still not be made, the individual's GP will be contacted to check contact details are correct. If these attempts do not result in contact being made within six weeks of loss of contact or the planned follow-up, a letter / email will be sent every month for three further months, asking the participant to re-establish contact if they are able to and advising that they will also be contacted again at the next follow-up point unless they advise otherwise. For any participant reluctant to complete the full outcome assessment at follow-up we will attempt to gain the CAPS-5 information as a minimum dataset.

As much information as possible will be collected from protocol non-adherers with a minimum of the primary and secondary outcome measures and reasons for non-adherence.

11 Trial Intervention

11.1.1 Spring – Internet Based Guided Self Help Programme

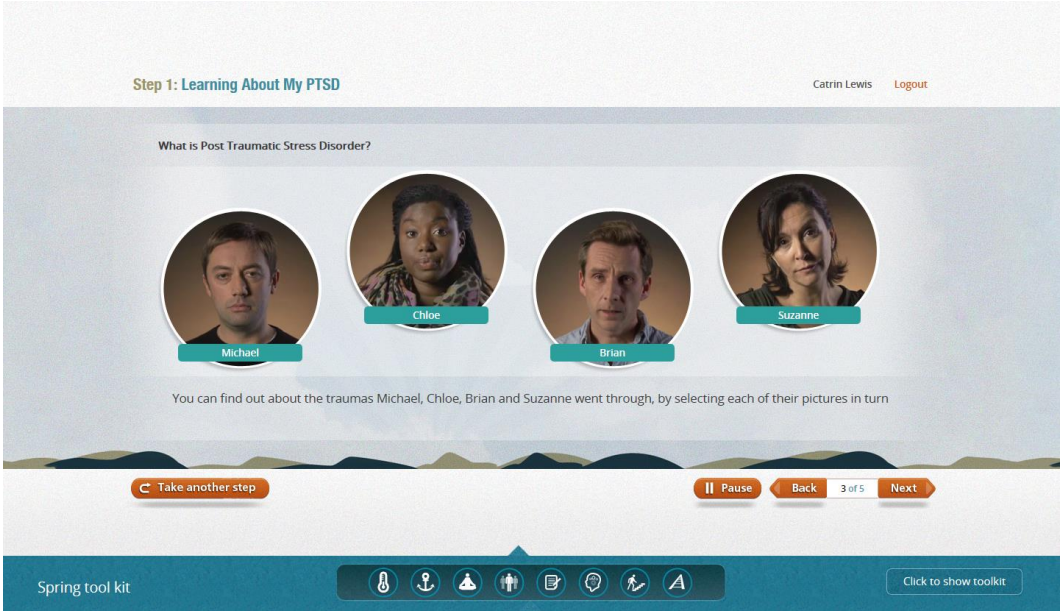
Guided Self Help Programme –The 8 week programme, entitled *Spring*, is based on the current standard treatment, TFCBT. It comprises eight steps (see Box 1). The therapist initially meets with the participant for an hour to develop a rapport and describe the programme. There are four subsequent fortnightly meetings of 30 minutes, undertaken face to face, via the internet or telephone according to participant preference. The modules are accompanied by homework. At each session, the therapist reviews progress and guides the participant through the programme. The aim of the guidance is to offer continued support, monitoring, motivation and problem solving. The eight online steps are usually completed in turn with some later steps relying on mastery of techniques taught in earlier steps. Each step provides psycho-education and the rationale for specific components of treatment. Each step activates a tool that becomes live in the *Toolkit* area of the website and aims to reduce traumatic stress symptoms. Everything entered into the toolkit becomes visible (with the participant's knowledge) to the therapist to facilitate input.

Box 1: PTSD Spring Steps

Step 1: Learning About My PTSD – Psychoeducation about PTSD illustrated by four actors describing their experience of PTSD to four different types of traumatic event.
Step 2: Grounding Myself - Explanation of grounding and its uses along with descriptions and demonstrations of grounding exercises.
Step 3: Managing My Anxiety – Education around relaxation with learning through videos of a controlled breathing technique, deep muscular relaxation and relaxation through imagery.
Step 4: Reclaiming My Life – Behavioural re-activation to help individuals return to previously undertaken/new activities.

Step 5: Coming to Terms with My Trauma – Provides rationale for imaginal exposure, narratives of the four video characters are provided. The therapist helps the participant to begin writing a narrative, which they complete remotely and read every day for at least 30 minutes.
Step 6: Changing My Thoughts – Cognitive techniques to address PTSD symptoms.
Step 7: Overcoming My Avoidance – Graded real life exposure work.
Step 8: Keeping Myself Well – This session reinforces what has been learnt during the programme, provides relapse prevention measures and guidance on what to do if symptoms return.

The screenshot below, taken from Step 1, shows the actors whose PTSD case histories are followed throughout the intervention. The toolkit can be seen at the bottom of the webpage.



The programme can be accessed online via a web browser or through an App. Participants will be able to use their PCs, tablets or smart phones to engage with the programme.

11.1.2 Trauma Focused Cognitive Behavioural Therapy (TFCBT) for PTSD

Trauma Focused Cognitive Behavioural Therapy (TFCBT) for PTSD is a face-to-face therapy of up to 12 sessions lasting 60-90 minutes that has been shown to be effective in randomised controlled trials in England[53],[54],[55] and Northern Ireland.[56] It is one of the standard treatments adopted by IAPT in England. It involves identifying the relevant appraisals, memory characteristics and triggers, and behavioural and cognitive strategies that maintain PTSD symptoms. TFCBT addresses these symptoms by:

- Modifying excessively negative appraisals of the trauma and/ or its sequelae.
- Reducing re-experiencing by elaboration of the trauma memories and discrimination of triggers.
- Dropping dysfunctional behaviours and cognitive strategies, particularly those related to avoidance of triggers for intrusive symptoms. These are strategies that have the immediate aim of reducing one's sense of current threat but have the long-term effect of maintaining the disorder, and are common in PTSD.

In-session treatment is augmented by homework assignments which patients are required to complete between sessions.

Trial therapists will be trained to deliver both interventions and there will be a manual for both interventions. Participants in both arms will complete outcome measures post-treatment at 16 weeks and 52 weeks post-randomisation, and the IES-R at each therapy contact.

11.2 Compliance

Participant adherence to the intervention will be measured by therapist records of the number of sessions, plus for those using GSH, the programme will record usage.

In order to ensure the interventions are delivered consistently and as planned, training, supervision and fidelity checks will be undertaken. In addition, participants will receive follow up contact following missed appointments to rearrange their session, maximising the likelihood of therapy completion.

Training: All therapists will receive training in the delivery of GSH for PTSD from co-investigators Dr Kitchiner and Dr Roberts, and refresher training of TFCBT for PTSD from co-investigator Professor Ehlers' team during a three-day training course that will include role-play. Following the training, and where possible, the therapists will see one training case for each intervention which will be audio recorded and reviewed by the co-investigators to confirm the therapists' competence to commence the trial interventions. Where local policy allows, the training case will be an actual service user with PTSD. Where this is not possible, the therapists may go through the intervention with a mock service user, for example, with a colleague acting as a service user.

Supervision: Dr Kitchiner and Dr Roberts will hold weekly supervision sessions in GSH for PTSD and TFCBT for PTSD for therapists throughout the intervention phase of the study. Not all therapists will attend all weeks but it is expected they will attend at least once per month when they are seeing participants. These will be conducted by telephone or online.

Fidelity Checking: Subject to the permission of participants, which will be checked and recorded at the start of the session, at least one intervention session for each participant will be audio-recorded. A sample will be randomly selected by the Trial Manager and will be checked for fidelity to the manual by independent experts with experience of the interventions. The TFCBT sessions will be rated using CT fidelity and competency rating scales used in previous RCTs of TFCBT. The GSH for PTSD sessions will be rated using bespoke fidelity and competency rating scales based on those developed for TFCBT, and supplemented by data on use of the programme generated by HCL.

Raters will be monitored for proficiency on the CAPS-5 scoring. They will be asked to rate a video of an actor being interviewed using the CAPS-5 and their ratings checked. Where the rater is consistently not in line with the other raters they will be given further training to ensure consistency of scoring.

12 Trial procedures

Following identification, as described above, potential participants will be contacted by a member of the research team who will describe the study and undertake a short telephone assessment to determine their eligibility for the study. This will include questions about symptoms and the inclusion and exclusion criteria and will last around 20 minutes.

If a potential participant appears to be eligible for inclusion, (s)he will be asked to monitor their PTSD symptoms for two weeks using a simple diary and an appointment made, at a convenient location for the potential participant, for a full face-to-face baseline assessment with a researcher at the end of that time. The Participant Information Booklet, details of the appointment and diary will be sent to the participant by e-mail or post.

At the face-to-face meeting, a researcher will undertake the full baseline assessment after having taken informed consent. This will involve administration of the primary and secondary outcome measures along with collection of demographic information and the Life Events Checklist (LEC-5)[57]. It will take 60-90 minutes. Subject to the participant being confirmed to meet the eligibility criteria, (s)he will be randomised to receive the GSH or TFCBT and a therapist allocated to deliver this. The researcher will arrange a 16 week follow-up appointment. To ensure continuity of the process for participants, the researchers will share with the therapist some brief details in a summary report. This will include responses on the Life Events Checklist (LEC-5), score on the CAPS-5 and answers to the risk assessment questions.

The researcher will inform the participant's GP by letter that they are taking part in RAPID. If the patient is ineligible or declines to take part, they will be referred (with their consent) back to the service that referred them to the study, or to their GP if they self-referred to the study.

The therapist will contact the participant and conduct the intervention, as described above, to be completed within 14 weeks of randomisation. These sessions will be audio-recorded for fidelity assessment. The therapist will perform a brief risk assessment at the start of the first session, in line with usual care and then conduct therapy as per the manual.

Follow-up assessments will occur at 16 weeks and 52 weeks post-randomisation at a convenient location for the potential participant, or by telephone. These assessments will include collection of all primary and secondary outcome measures along with additional information regarding service utilisation. They will last 60-90 minutes.

Process evaluation will be undertaken alongside the trial, in accordance with recent MRC guidance to explore factors impacting on intervention delivery and outcome. This will explore context, reach, fidelity, exposure, recruitment, retention and adherence using both quantitative (sessions attended, demographic characteristics, fidelity checklist) and qualitative methods (participant and therapist interviews). Qualitative interviews will also explore factors influencing acceptability of treatments offered. A proportion of participants would complete a qualitative interview with a researcher before they start treatment and after they have finished treatment. These interviews will last 60-90 minutes, explore participants' views of the two treatments and will be audio-recorded.

Participants will be offered a £20 shopping voucher on completion of the 16 week and 52 week follow-up assessment as a token of appreciation for their participation in the study.

12.1 Assessments

All assessments will be conducted by a researcher trained in rating the outcome measures. They will be blind to randomisation and participants will be asked not to reveal their allocation. The initial telephone screening assessment will ensure that the inclusion criteria 1-3 and exclusion criteria are satisfied. Participants will then be asked to monitor their symptoms for two weeks using a daily dairy (previous studies have found that this results in significant reduction in symptoms for some PTSD sufferers). The face-to-face baseline assessment will occur after this and will collect demographic and other baseline data as well as assessing inclusion criteria 4-6 and re-checking inclusion criterion 2 (single event) and exclusion criterion 7; those who continue to fulfil the eligibility criteria will be randomised to one of the two groups: GSH for PTSD or TFCBT for PTSD. Follow up will occur 16 weeks (+ / - two weeks) and 52 weeks (+ / - one month) after randomisation. This will involve re-administration of all the outcome measures and may be conducted face-to-face or on the telephone. The IES-R, PHQ-9 and GAD-7 will be administered at each therapy session throughout the intervention to aid clinical feedback. The IES-R results will be also be recorded for research purposes for an ongoing measure of PTSD.

Table 2. Schedule of enrolment, interventions and assessments

Procedures	Initial telephone PTSD Screen	Baseline	GSH Therapist sessions	TFCBT for PTSD sessions	Follow Up at 16 weeks	Follow Up at 52 weeks	As occurs
Eligibility Assessment	Inclusion Criteria 1-3 Exclusion Criteria	Inclusion Criteria 2 (single event), 4-6					
Informed consent		X					
Demographics		X					
LEC-5		X					
CAPS-5		X			X	X	
IES-R		X	4-5	8-12[1]	X	X	
WSAS		X			X	X	
PHQ-9		X			X	X	

[1] Some additional measures may be given before each treatment session as part of standard clinical care but will not be used for research purposes

GAD-7		X			X	X	
AUDIT-O		X			X	X	
ISI		X			x	X	
MSPSS		X			X	X	
EQ-5D-5L		X			X	X	
Adapted CSSRI-EU		X			X	X	
PTCI		X			X	X	
GSES		X			X	X	
CSQ-8					X		
ARM-5			X (3rd week)	X (3rd week)	X		
Randomisation		X					
Delivery of intervention			4-5	8-12			
Compliance			X	X	X		
Adverse event assessments							X
Therapists Withdrawal Checklist							X

All assessments should be conducted as close to the due date as possible but certainly within two weeks of the due date. However, to ensure a full a data set as possible, we will include data collected beyond this time period and record how many are outside this time window.

12.2 Follow-up

Outcome measures will be collected at 16 weeks and 52 weeks post-randomisation. The IES-R will also be collected and recorded for research purposes at each therapy contact.

13 Safety reporting

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and safety specialist unless the SAE is specified as not requiring immediate reporting (see section 13.2). Refer to section 10.1 to see if the participant also needs to be withdrawn.

13.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant and which are not necessarily caused by or related to that product
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

** **Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

*** **Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE 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.

13.2 Trial Specific SAE Reporting/Risk of Harm

In addition to the SAE reporting requirements above, for the purposes of this trial severe self-harm and harm to others must be reported. Therapists will be asked to notify the study team directly should they be concerned at any time that a participant has, or is likely to cause significant harm to themselves. The therapist should also inform the participant's GP. Therapists will be asked to inform the appropriate authorities directly should they become concerned at any time that a participant has, or is likely to cause significant harm to others.

This information should be recorded in the participant's notes and emailed to the CTR trial team (rapid@cardiff.ac.uk) using the Participant Identification Number (PID) (not identifiable information) within 24 hours.

Please also refer to the withdrawal section (10) to determine whether the participant needs to be withdrawn.

13.3 Causality

Causal relationship will be assessed for the intervention and procedures:

Intervention: GSH programme or individual TFCBT
Procedures: Research assessments

The Principal Investigator (or another appropriately qualified delegated therapist from the trial team) will assess each SAE to determine the causal relationship and the Chief Investigator (or another appropriately qualified therapist/psychiatrist from the Trial Management Group) can also provide this assessment where necessary:

Relationship	Description	Reasonable possibility that the SAE may have been caused by the intervention?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No

Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after the intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after the intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

13.4 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness.

The expectedness assessment should be made according to the intervention information as detailed in the protocol (11.1.1 & 11.1.2).

Reference Safety Information (RSI)

The only expected side effect of either intervention which may occur in some instances is an increase in distress as a result of exposure to the trauma.

Expectedness decisions must be based purely on the content of the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described in the RSI is considered unexpected.

Reference Safety Information (RSI) on any CTR trial will be reviewed regularly according to CTR procedures.

13.5 Reporting procedures

13.5.1 Participating Site Responsibilities

The PI (or appropriately qualified delegated therapist from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

SAE Fax number:

0203 0432 376

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 30 days after the participant receives the intervention.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately qualified member of the trial team as registered on the delegation log).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 16.

13.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 30 days after the participant receives the last part of the intervention.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

13.6 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

14 Statistical considerations

14.1 Randomisation

Individual randomisation will be performed by CTR and will be conducted using an online minimisation algorithm developed by CTR in accordance with CTR SOPs. The ratio will be 1:1. Minimisation will ensure balance between trial arms for gender, but will retain a random element and will be stratified by research centre. Randomisation details will be emailed to CTR who will aim to randomise the participant the next working day. Allocations will be communicated to the local PIs/therapists.

14.2 Blinding

It is not possible to blind the therapists or the participants given the complex interventions under investigation. However, the outcome assessors will be blind to treatment allocation and the therapists and participants will be asked not to discuss their allocation with the assessor. This will be stressed at the start of the interview and will minimise any potential bias the assessor may have when conducting the outcome assessments. To measure the success or otherwise of allocation concealment, the researchers will be asked to guess the participant's allocation before and after each assessment. This will be recorded and compared to chance at the end of the study.

14.3 Sample size

As the study aims to show non-inferiority of GSH for PTSD compared to TFCBT, the power calculation considers the non-inferiority margin as opposed to the effect size. The non-inferiority margin will be 5 points on the 80 point CAPS-5[1] scale, with a common standard deviation of 10.3. A recent meta-analysis[12] indicates that the standardised mean difference between TFCBT and waitlist/usual care for the treatment of PTSD is -1.62. This corresponds to 16.6 points on the CAPS-5. This means that if we demonstrate one-sided non-inferiority to within 5 points of the gold standard, we will also demonstrate superiority over wait list/usual care in line with ICHE9 guidance for non-inferiority studies.[58, 59] Pilot work has been done indicating an ICC of 5.6% at the therapist level at 10 weeks. At 22 weeks, however, there was no observable clustering of CAPS-5 scores amongst therapists. Given our primary outcome (CAPS-5) is measured at 16 weeks we have allowed for 1% clustering and recalculated the sample size. We allow for 20% attrition. On the basis of the anticipated average therapist cluster size being four, the design effect is 1.03, requiring a 3% inflation of the sample size. This results in a final sample size of 192 (inflated from 186) which provides 90% power (nQuery v7.0) with a one-sided 5% significance level.

For the qualitative study, the sample size will be guided by preliminary analysis and constant comparison (comparing and contrasting themes from other interviews) during each data collection phase, until the research team is satisfied that there is data saturation and no new themes which are important to the research question arise.[60] However, it is helpful to have a guide to sample size for study planning. Based on previous research,[9] we propose that interviews will be conducted with around 10-20 participants and around 8 therapists purposefully sampled from the four different geographical sites.

14.4 Missing, unused & spurious data

Details are provided in the Statistical Analysis Plan (SAP).

14.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

14.6 Termination of the trial

There are no stopping rules for the trial as it is a low risk non-CTIMP.

14.7 Inclusion in analysis

The analysis will be intention to treat (ITT) and so all randomised patients will be analysed.

15 Analysis

15.1 Main analysis

The primary analysis will be performed using analysis of covariance, modelling 16 weeks follow-up CAPS-5 score controlling for baseline CAPS-5 score, research centre and important patient characteristics: gender, co-morbid depression and time since trauma. Reflecting the sample size calculation, analyses will be undertaken with 2-level hierarchical models with patients clustered within therapists. The primary analysis will utilise multiple imputation with interim collected IES-R scores as auxiliary variables to the imputation. Given that IES-R is likely to be collected 4-5 times for GSH arm patients and 8-12 times for TFCBT-for-PTSD arm patients, there will be bias created by undertaking any multiple imputation model. For this analysis, we will apply a different imputation model to each arm: both containing the relevant number of auxiliary variables (along with baseline CAPS-5 score, research centre, gender, age and time since trauma and clustered by therapist). Imputed datasets will then be combined before undertaking analyses. The results will be summarised using point estimates, and 1-sided 95% confidence intervals and p-values (in line with the sample size calculation). Since this is a non-inferiority design, we will be checking whether the confidence interval for the difference between arms lies entirely within the 5 point non-inferiority margin. Where the treatment effect and 1-sided 95% confidence interval is entirely greater than 0 then superiority will be assessed with a 2-sided 90% confidence interval and relevant p-value.[61]

For the primary outcome, the complete case intention to treat analysis and per-protocol analysis are both of scientific interest and will be reported as sensitivity analyses under a non-inferiority framework. [62]

A further sensitivity analysis of the primary outcome under a non-inferiority framework will implement a different multiple imputation model: IES-R scores taken from 5 clinic visits for the TFCBT-for-PTSD arm patients that align similarly in time to those of the GSH arm patients will be used as auxiliary variables in an imputation model (this one with both arms combined) along with baseline CAPS-5 score, research centre, gender, age and time since trauma and clustered by therapist.

A further sensitivity analysis will account for patient adherence to the protocol using complier adjusted causal effect (CACE) analysis.[63]

Secondary outcomes include: CAPS-5, EQ-5D-5L, WSAS, PHQ-9, GAD-7, AUDIT-O, MSPSS, IES-R, ISI, GSES, PTC, adapted CSSRI-EU and CSQ-8. These are all continuous measures and will be analysed using multiple imputation to account for missing data under a non-inferiority framework. . Transformations will be explored to improve model fit if distributional assumptions are not satisfied. This will be assessed by visual inspection and formal fit statistics compared to decide on the transformation chosen.

In the cases of all multiple imputation models, we will explore whether the baseline version of the outcome, research centre, gender, co-morbid depression and and time since trauma are associated with the missingness of the outcome. Multiple imputation will always be undertaken but we will note where these explorations suggest that the mechanism is missing not at random. IES-R scores over time will be explored using a hierarchical modelling (including clustering by therapist if this is identified in the primary analysis) and an appropriate covariance structure allowing for IES-R scores within an individual to be correlated over time. This will facilitate the fitting of IES-R trajectories over time (since randomisation) interacted with intervention arm, whilst also controlling for the same covariates as the primary analysis. Note that these are likely collected 4-5 times for GSH arm patients and 8-12 times for TFCBT-for-PTSD arm patients.

All analyses will be performed in the stata programming language and environment, with REALCOM software used for multi-level multiple imputation, and SPSS for initial storage and data manipulation. A detailed statistical analysis plan will be signed off (by trial statistician, chief investigator, CTR MBN Director and co-applicant statistician) before final primary analysis data collection finishes, in line with CTR standard operating procedures (SOPs).

15.1.1 Sub-group & interim analysis

No interim analyses are planned. We will explore differences in treatment effects by gender in a sub-group analysis by including an interaction term between treatment arm and gender.

15.2 Qualitative analysis

The data will be analysed using framework analysis.[64] This is a systematic five-stage method, which is increasingly being used in health care research.[65] It will allow us to compare themes across time point, treatment centre, and interviewee category (i.e. patient and therapist). We will identify contradictory data, as points of contrast as well as similarities will be important in order to understand uptake of the GSH tool. The method is well defined and allows for greater transparency. Vital measures will be put into place to ensure validity and reliability. More than one person will be involved in the analysis and double coding will be carried out until consensus is reached. The framework analytic approach has been selected as it is a recognised transparent analytic approach. This qualitative component has been designed using the principles of the Critical Appraisal Skills Programme qualitative checklist, to ensure the quality of qualitative research.[66]

We will also conduct in-depth interviews with key stakeholders (n=4). Using a topic guide, we will explore issues relating to commissioning and barriers that may impact on the successful roll-out of a new intervention, looking particularly at contextual factors relevant for different areas and service provisions.

15.3 Cost-effectiveness analysis

An economic evaluation will be conducted from the perspective of the UK NHS and personal, social services. To determine the cost-effectiveness of GSH versus TFCBT, and the extent to which it can be regarded as representing value for money, two analyses will be undertaken – one will assess the relative cost-effectiveness by estimating the incremental costs of achieving changes in relevant natural units of outcome that commissioners, health care professionals, public health decision makers and service users find relevant (e.g. incremental cost of achieving a percentage improvement in PTSD symptoms). This will be established through consultation with the service users and commissioners supporting the study. The second analysis will comprise a cost-utility analysis using the EQ-5D-5L utilities to estimate the incremental costs per quality adjusted life year (QALY) gained as required by NICE in the reference case.[67]

The contributions associated with the GSH in relation to staff time and costs associated with training of therapists, along with materials and equipment used in the process associated with GSH development and implementation, will be collected during the trial by consultation with relevant staff, logged in physical units and translated into costs using published unit costs (e.g. Curtis L. and Burns A., Unit Costs of Health and Social Care, 2015).[68] Resource utilisation of services prior to the GSH implementation, as a result of the intervention, and at follow-up relative to the control group, will be measured using an adapted CSSRI-EU. Net incremental cost will be computed and used in conjunction with CAPS-5 and other outcome measures to produce a series of cost-effectiveness ratios, while it will be used with EQ-5D-5L utility scores to generate an estimate of cost per QALY gained.

The QALY gains will also be used in a net–benefit analysis based on accepted NICE 'value for money' thresholds. As the follow-up is at 52 weeks, no costs and outcomes will be subjected to discounting. Uncertainty around the cost and effectiveness estimates will be investigated by: probabilistic sensitivity analysis, using the incremental cost per QALY as the metric for this assessment measured against the NICE range of 'value for money' thresholds between £20k and £30k per QALY gained, represented by cost-effectiveness acceptability curves;[69] a series of one-way sensitivity analyses to assess the impact of parameter variation on baseline estimates of the range of incremental cost-effectiveness ratios; and a set of alternative scenarios will be constructed, based on the findings from relevant studies of CBT for PTSD[53-56] to compare the relative cost-effectiveness of GSH against different durations of CBT and supportive care.

In addition to a trial-based analysis, longer-term cost-effectiveness will be assessed using decision analytic modelling methods. The derived model, based on a review of published models at the time of the analysis, will use parameter estimates derived from the trial and information from literature sources relating to long-term effects of PTSD alongside other sources, to arrive at meaningful long-term estimates of cost-effectiveness and budget impact. A detailed health economic analysis plan will be signed off before recruitment finishes.

15.4 Process Evaluation

A process evaluation conducted alongside the main trial will explore contextual factors and mechanisms of change that may impact on effectiveness and successful rollout of the intervention post-trial. Specifically, we will examine the contextual factors surrounding intervention delivery, which will include assessment of recruitment, retention, fidelity and adherence. The process evaluation will be developed according to the MRC guidance and will make use of both quantitative data (including fidelity measurement, retention, adherence rates, time spent on different steps of the GSH programme) and qualitative data as outlined above. We will sample therapists and patients to be invited to take part in two qualitative interviews per-intervention and post-intervention. Other stakeholders will also be identified and invited to take part in a qualitative interview to further examine issues of sustainability and roll-out. Detailed information regarding whether the intervention was delivered as intended (fidelity) and the quantity of the intervention implemented (dose) will allow us to test the theorised mechanism of effect of GSH for PTSD (a combination of: psycho-education about PTSD; imaginal and in-vivo exposure work to achieve habituation to distressing images and avoided situations; cognitive work to identify and modify negative/distorted cognitions; and stress management skills to cope with anxiety and other symptoms) and whether certain factors appear to be more important than others.

A therapist training & support sub-study will explore whether therapist-rated service support for TFCBT affects the quality of TFCBT sessions delivered in clinical practice. RAPID therapists will be asked to complete a questionnaire, and in conjunction with the TFCBT session fidelity assessments, the data generated will be analysed in order to explore factors extraneous to the research study (including individual training and, service support for CBT) which may influence the quality of CBT sessions delivered in routine clinical practice. Therapists will be offered a £10 voucher to thank them for their participation.

16 Data Management

Source data will be captured online via a bespoke online system developed within the CTR. Access to the system will be restricted to named study personnel only and via a secure login and password. The system will be roles-based with restricted read/write/edit permissions. Any changes made to the data will be stored in the audit log within the system's database with a full history of changes being recorded. The system will be accessible via any online PC, tablet or mobile device. Data will be stored securely on a secure server.

Data quality will be maintained through a series of field and form-level validations which restrict what users are able to enter. This will help maintain data quality throughout the duration of the data collection phase. In the event of source data being collected on paper, an exact copy of the data will be manually entered into the database with the electronic record being verified against the paper record.

The system will be designed, built and maintained in line with the appropriate CTR SOPs. The study's data management processes will also be undertaken in line with the appropriate CTR SOPs.

16.1 Completion of CRFs

Where possible, all CRF's will be completed online. In the event of the system being unavailable, or lack of access to the internet, paper versions of the CRF's will be used instead with the paper record then manually entered into the database. Once entered the paper copy will be returned to the RAPID team at the CTR and the data will be verified by a person other than that who entered the data.

17 Translational research or sub trial

In order to maximise the potential of the information collected through RAPID, participants will be invited to join the National Centre for Mental Health (NCMH) study. This study has over 6,500 participants and is designed to help understand why some people experience problems with their mental health in order to improve understanding of conditions such as PTSD and help find better treatments in the future. If participants decide to join the NCMH study, the information collected through RAPID will be added to the NCMH dataset. Participants may then be invited by NCMH researchers to complete further questionnaires or consider taking part in other studies at a later date. There will be no obligation to do so. Participants will also be asked for permission to link their data in an anonymous format to routinely collected, anonymised datasets, e.g. the Secure Anonymised Information Linkage (SAIL) dataset at Swansea University. All data linkage is undertaken in line with the Data Protection Act (1998) and University governance.

18 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the RAPID team at the CTR in writing as soon as they become aware of it. Issues of non-compliance will be processed in accordance with the CTR SOPs.

19 End of Trial definition

The treatment phase will be followed by a non-interventional follow-up period which will continue for 52 weeks after the last participant has been randomised.

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as last participant, last data collection.

The Sponsor will notify the main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

20 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

21 Regulatory Considerations

21.1 Ethical and governance approval

This protocol has received approval Wales REC 3, a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

The most significant ethical issue is the possibility of causing participants upset. We will follow good practice guidelines to minimise the risk of this occurring and to manage any distress that does occur. Research staff will be experienced mental health professionals or researchers. All members of research staff will participate in regular supervision delivered by a senior mental health professional. If significant distress is caused, participants will have access to quick and appropriate clinical input. Therapists can recommend that the participant is withdrawn from the trial if necessary.

21.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the Data Protection Act 1998. The data custodian and the translational sample custodian for this trial is Cardiff University.

21.3 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity.
- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

Where participants are recruited at NHS sites and the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

21.4 Trial sponsorship

Cardiff University will act as Sponsor for trial. Delegated responsibilities will be assigned to the CTR and to sites taking part in this trial. These are listed on the trial delegation logs and held within the Trial Master File at the CTR.

21.5 Funding

Research funding of £1,258,936 has been awarded by the National Institute for Health Research Health Technology Assessment Scheme to Cardiff University to cover research costs. Funding has also been made available through excess treatment costs to cover therapist training and maintenance of the website and app. Support costs will be covered by the Health and Care Research Wales Support and Delivery Service in Wales and the NIHR Clinical Research Network in England. The NIHR will contract manage Cardiff University to deliver the project.

22 Trial management

22.1 TMG (Trial Management Group)

A TMG will be established and meet monthly. The TMG will include the Chief Investigator (CI), all other investigators, and central project team (trial and data managers, trial administrator, statistician) to discuss the progression and day-to-day management issues of the trial. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

22.2 TSC (Trial Steering Committee)

A TSC will be established and meet at least annually. The TSC will comprise of an independent chair who has expertise in both trials and GSH/PTSD and three other independent members including a user representative who has had lived experience with PTSD, a statistician and a clinician working with people with PTSD. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

22.3 DMC (Data Monitoring Committee)

The TSC determined at their first meeting that a DMC is required. The DMC will be comprised of at least three members to include one clinician experienced in the clinical area and one statistician. The remit of the DMC will be to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

23 Quality Control and Assurance

23.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the RAPID trial. Low monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

23.2 Audits & inspections

The trial is subject to inspection and audit by Cardiff University under their remit as Sponsor.

24 Publication policy

All publications and presentations relating to the trial will be authorised by the Trial Management Group and adhere to the study's publication policy.

To achieve the goals of RAPID, adequate promotion, exploitation and communication is a critical requirement. Promotion will start at the beginning of the project; early activities will include finalising a strategic dissemination plan, promotion and awareness raising. The "living" plan will be informed through an ongoing dialogue with stakeholders and updated and improved through evaluation, new developments, comments, reactions, suggestions, needs and preferences.

Findings will be disseminated widely using a variety of tailored methods targeting specific audiences. A summary report of trial results written in lay-language will be sent to study participants and other key stakeholders. The report will also be displayed and available at venues used for recruitment. We will hold informal patient-centred meetings at each trial site, to present the results orally and allow time for questions and clarification. We will also hold an open conference at each centre in the final month of the project. If the outcome is positive, the conferences will include free training in the GSH programme for NHS staff coupled with free access to the programme for a certain number of therapeutic encounters. We will send reports of trial results to NHS commissioners, outlining the cost-saving potential of GSH and the scope for improving routine clinical practice for PTSD. We will disseminate the findings publicly through news items on the NCMH website (www.ncmh.info), which attracts an average of 2250 unique visitors each month, and an article in the widely circulated NCMH newsletter.

We will publicise the trial results through social media and publish posts related to trial progress and results on the NCMH blog-site, which features posts that have attracted up to 10,000 hits. We have experience of successfully engaging local and national media and will work with the NCMH communications team to formulate strategies for press releases and the dissemination of findings through newspaper articles and radio features. We will work with knowledge brokers, such as the Science Media Centre, to maximise coverage. Study outcomes will be presented to the academic community at national and international conferences by means of oral presentation, poster presentation, and interactive workshops. We will target conferences likely to be attended by large numbers of therapists and managers working in IAPT and other primary and secondary care NHS psychological treatment services (e.g. BABCP, BACP and UKPTS). We will also disseminate to the third sector and other services likely to deal with individuals with PTSD who could potentially benefit from treatment (e.g. MIND, SARCs, Victim Support). We aim to publish the quantitative, qualitative and health economic results in high impact open-access, peer reviewed journals such as the British Medical Journal. A complete account of the research will also be published in the NIHR HTA Journal. We expect at least three high impact peer reviewed publications and six conference presentations.

All the dissemination and promotion activities will be supported by project specific webpages on the NCMH website. The webpages will include descriptions of the project, its progress and achievements in plain and scientific language, press releases and announcements of and registration for conferences and training events. External evaluation of dissemination plans, including the identification of successful implementation strategies and barriers to implementation among end users (e.g. PTSD sufferers, health service planners and managers, clinicians, clinical professional bodies, etc.) will be undertaken by the TSC.

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