Trial Protocol

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VERSION CONTROL DOCUMENT

PROTOCOL: Multisite Randomised Controlled Trial of Trauma-Focused Cognitive Behaviour Therapy for psychosis to reduce post-traumatic stress symptoms in people with co-morbid post-traumatic stress disorder and psychosis, compared to Treatment as Usual: **the STAR** (**S**tudy of **T**rauma **A**nd **R**ecovery) **trial**

VERSION No.	DATE	DATE APPROVED BY HTA	DATE APPROVED BY DMEC/TSC	DATE APPROVED BY R&D	DATE APPROVED BY REC/HRA	DATE IMPLEMENTED	COMMENTS e.g. reason for change, stage of study, status (draft or track changes visible), date sent to co-Is or participating sites, acknowledgement of receipt, etc
1.00	26th February 2020	10/03/2020					Trial name changed from **TRUST** (**Tr**a**u**ma and P**s**ychosis **T**herapy) to **STAR** (**S**tudy of **T**rauma **A**nd **R**ecovery) Trial
1.01	30th April 2020						Track-changes visible, minor changes following R&D review + COVID-19 related delay
1.02	1st May 2020		1/05/2020				Sent to DMEC/TSC
1.03	28th May 2020			28/05/2020			Given R&D approval; 28/05/2020 submitted to HRA 29/05/2020
2.00	17th July 2020				24/07/2020		Track-changes visible, changed following HRA/REC review

2.01	22nd July 2020	16/09/2020		20/08/2020			Track changes visible for COVID amendment (minor amendments)
2.02	28th July 2020	16/09/2020	26/08/2020	26/08/2020			Substantial amendment (short ASIQ; WAI)
2.03	8th September 2020	16/09/2020					Change from short ASIQ to Paykel Suicidal Feelings Scale
2.04	17th September 2020	17/09/2020	9/10/2020	28/09/2020	30/09/2020	12/10/2020	Clarifications re PTSD eligibility criteria for KCTU
2.05	20th November 2020	03/12/20	9/10/2020	11/12/20	17/12/20	18/12/20	Appendix added for EME-funded add-on study: "How does the STAR therapy affect the mind and brain?" Following TSC/DMEC, minor changes to Adverse Events/Serious Adverse Events section; clarification added to operationalize trauma-focused therapy in exclusion criteria; Clarification that therapy adherence progression criteria in Appendix 2 relates to independent tape ratings
2.06	16/02/21	N/A (EME study only)		11/12/20	17/12/20	22/01/21	Temporary change in procedures for our EME add-on study (appendix 7), to allow for remote collection of behavioural data for the

							MRI component – **no longer in effect**
2.07	25/03/21	N/A (EME study only)		22/04/21	27/04/21	27/04/21	Option added in procedures for our EME add-on study (appendix 7), to allow for participants to consent to fMRI procedures only
3.00	28/06/21						Clarification re timing of analyses and adding of reliable change for CAPS-5; adding 3 categories to the 'other modalities' PSYRATs
3.01	18/08/21	N/A (EME study only)	21/09/21	24/09/21	29/09/21	05/01/22	Change to EME protocol (appendix 7), adding an additional scanning site (Newcastle University)
3.02	21/01/22	27/01/22	23/02/22	17/02/22	24/02/22	24/02/22	Addition of PIC sites as potential source of recruitment
3.03	05/09/22	N/A (EME study only)	Initial approval (by email): 29/08/22 Final approval: 24/10/22	13/09/22	23/09/22	26/09/22	Change to EME protocol (appendix 7). Memory task in scanner increased by 5 minutes at 9-months follow-up timepoint to include an everyday memories comparison condition; honorarium increased for participants completing follow-up at both timepoints
3.04	28/10/22	03/11/22	28.06.22	24/11/22	29/11/22	11/01/23	Change to recruitment end date (to April 2023). Change from indicating WAI

							collected at 3 timepoints (now only 2)
3.05	22.03.24		20.05.24	10.04.24	13.05.24	03.06.24	Update to EME protocol appendix to v1.09. Update regarding Secondary Hypothesis E3, and retrospective explanation of the exclusion of the neutral faces condition in the fMRI social threat (emotional faces) task. Refinement of 'case examples' therapy dissemination plans.

Contents

N.B. This protocol has been written according to the journal TRIALS manuscript submission guidance. Any numbers in curly brackets (e.g. {51}) relate to item identifiers from the SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. It is important that they remain in the document to allow electronic searches by SPIRIT item number. Sections marked "N/A" have been left in intentionally.

Title

Multisite Randomised Controlled Trial of Trauma-Focused Cognitive Behaviour Therapy for psychosis to reduce post-traumatic stress symptoms in people with co-morbid post-traumatic stress disorder and psychosis, compared to Treatment as Usual: **the STAR** (**S**tudy of **T**rauma **A**nd **R**ecovery) **trial**

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Abstract

Background: People with psychosis have high rates of trauma, with a post-traumatic stress-disorder (PTSD) prevalence rate of approximately 15%, which exacerbates psychotic symptoms such as delusions and hallucinations. Pilot studies have shown that trauma-focused (TF) psychological therapies can be safe and effective in such individuals. This definitive trial, the largest to date, will evaluate the clinical effectiveness of a TF therapy integrated with Cognitive Behaviour Therapy for psychosis (TF-CBTp) on post-traumatic stress symptoms in people with psychosis. The secondary aims are to: compare groups on cost-effectiveness; ascertain whether TF-CBTp impacts on a range of other meaningful outcomes; determine whether therapy effects endure; determine acceptability of the therapy in participants and therapists.

Methods: Rater blind, parallel arm, pragmatic Randomised Controlled Trial comparing TF-CBTp +Treatment As Usual (TAU) to TAU only. Adults (N=300) with distressing PTSD and psychosis symptoms from five mental health Trusts (60 per site) will be randomized to the two groups. Therapy will be manualized and last 9 months (m) with trained therapists. We will assess PTSD symptoms (primary outcome); percentage who show loss of PTSD diagnosis and clinically significant change; psychosis symptoms; emotional well-being; substance use; suicidal ideation; psychological recovery; social functioning; service use costs; a total of four times: before randomisation; 4m (mid-therapy); 9m (end of therapy; primary end point); 24m (15m after end of therapy) post-randomisation. Four 3-monthly phone calls will be made between 9m and 24m assessment points, to collect service-use over the previous three months. Therapy acceptability will be assessed through qualitative interviews with participants (N=35) and therapists (N=5-10). An internal pilot will ensure integrity of trial recruitment and outcome data, as well as therapy protocol safety and adherence. Data will be analysed following intention-to-treat principles using generalised linear mixed models and reported according to Consolidated Standards of Reporting Trials-Social and Psychological Interventions Statement.

Discussion: The proposed intervention has the potential to: provide significant patient benefit in terms of reductions in distressing symptoms of post-traumatic stress, psychosis, and emotional problems; enable clinicians to implement trauma-focused therapy confidently in this population; and be cost-effective to service providers through reduced service use.

Trial registration: ISRCTN93382525

Keywords

Post-traumatic stress disorder (PTSD); psychosis; schizophrenia-spectrum disorder; trauma; cognitive behaviour therapy; trauma-focused therapy; trauma memory reprocessing; delusions; hallucinations

Abbreviations

AD-SUS: Adult Service Use Schedule
AEs: Adverse Events
A&L: Assessment and Liaison services
ASSIST: Alcohol, Smoking and Substance Involvement Screening Test
AT: Assessment and Treatment services
CAPS-5: Clinician-Administered PTSD Scale for DSM-5
CBT: Cognitive Behaviour Therapy
CBTp: Cognitive Behaviour Therapy for psychosis
CCGs: Clinical Commissioning Groups
CDSS: Calgary Depression Scale
CHOICE: CHoice of Outcome In Cbt for psychoses
CI: Confidence Interval
CI: Chief Investigator
CMHTs: Community Mental Health Teams
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-SPI: Consolidated Standards of Reporting Trials – Social and Psychological Interventions
CRIS: Clinical Record Interactive Search
CRN: Clinical Research Network
CTS-R: Cognitive Therapy Scale – Revised
CTU: Clinical Trials Unit
C4C: Consent for Contact
DASS-21: Short form of the Depression Anxiety Stress Scales
DSPS: Dissociative Subtype of PTSD Scale
DMEC: Data Management and Ethics Committee
DNA: Did Not Attend
DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5th Edition
EDC: Electronic Data Capture
EIP: Early Intervention for Psychosis
EQ-5D-3L: EuroQol 3-dimensions
EQ-5D-5L: EuroQol 5-dimensions
ES: Effect Size
FU: Follow-Up
GDPR: General Data Protection Regulation
GP: General Practitioner
GCP: Good Clinical Practice
GPTS-R: Revised Green et al Paranoid Thoughts Scale
HEIs: Higher Education Institutions
HRA: Health Research Authority
HTA: Health Technology Assessment
IAPT-SMI: Improving Access to Psychological Therapies for Severe Mental Ilness
ICCs: intraclass correlation coefficients

ICD-10: International Classification of Diseases 10th Edition
ICD-11: International Classification of Diseases 11th Edition
ICH: International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IT: Information Technology
ITQ: International Trauma Questionnaire
ITT: Intention To Treat
KCL: King's College London
KCTU: King's Clinical Trials Unit
MRC: Medical Research Council
m: months
N: number
NHS: National Health Service
NHS-E: NHS-England
NICE: National Institute for Health and Care Excellence
NIHR: National Institute of Health Research
PCL-5: PTSD Checklist for DSM-5
PCMHTs: Primary Community Mental Health Teams
PI: Principal Investigator
PICuP: Psychological Intervention Clinic for outpatients with Psychosis
PID: Personally Identifiable Data
PPI: Patient Public Involvement
PSFS: Paykel Suicidal Feelings Scale
PSP: Personal and Social Performance Scale
PSSRU: Personal Social Services Research Unit
PSYRATS: Psychosis Symptom Rating Scales
PTCI: Posttraumatic Cognitions Inventory
PTSD: Post Traumatic Stress Disorder
PT-SMI: Psychological Therapies for Severe Mental Illness
QALYs: Quality Adjusted Life Years
RCT: Randomised Controlled Trial
R&D: Research & Development
REC: Research Ethics Committee
ReQoL: Recovering Quality of Life
RWs: Research Workers
SAEs: Serious Adverse Events
SD: Standard Deviation
SLaM: South London and Maudsley NHS Foundation Trust
SMI: Severe Mental Illness
SREs: Serious Related Events
SURG: Service User Research Group
TALE: Trauma And Life Events Checklist
TAU: Treatment As Usual
TF-CBT: Trauma-Focused Cognitive Behaviour Therapy
TF-CBTp: Trauma-Focused Cognitive Behaviour Therapy for psychosis
TMC: Trial Management Committee
TRUST trial: **Tr**a**u**ma and p**s**ychosis **t**herapy trial
TSC: Trial Steering Committee
UK: United Kingdom
USREs: Unexpected Serious Related Events

WHO: World Health Organisation
≥: equal to or above

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Multisite Randomised Controlled Trial of Trauma-Focused Cognitive Behaviour Therapy for psychosis to reduce post-traumatic stress symptoms in people with co-morbid post-traumatic stress disorder and psychosis, compared to usual treatment: **the STAR** (**S**tudy of **T**rauma **A**nd **R**ecovery) **trial**
Trial registration {2a and 2b}.	ISRCTN93382525
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Author details {5a}	See below
Name and contact information for the trial sponsor {5b}	See below
Role of sponsor {5c}	This trial was designed by the research team in response to a commissioned call from the Funder (NIHR), who has also approved the content of the final research protocol. Neither the Funder nor the Co-Sponsors will have a role in data collection, management, analysis, or interpretation; nor in the writing of the final report or decision to submit the report. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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Introduction

Background and rationale {6a}

People with psychosis report high rates of adversity and trauma, particularly interpersonal victimisation (e.g. emotional, physical, and sexual abuse/assaults) both in childhood and adulthood, with the majority having experienced multiple traumas (75-98% of those reporting trauma; (1)). The prevalence rate of Post-Traumatic Stress Disorder (PTSD) in this population is approximately 15%, which is up to five times the general population rates(2). PTSD is characterised by intrusive memories of the trauma, such as 'flashbacks', hyperarousal, and avoidance of trauma reminders, and post-traumatic symptoms are frequently intertwined with psychotic symptoms, such as delusions and hallucinations (3, 4). However, in clinical practice PTSD is overlooked in many people with psychosis (2). A single diagnosis often means that the psychosis is treated pharmacologically, but not the psychological effects of traumatic events. Such individuals have a poorer response to antipsychotic medication (5), and increased substance-abuse, self-harm, suicide behavior, and psychiatric and medical hospitalization, than those with psychosis alone (1).

Cognitive Behavioural Therapy for psychosis (CBTp) is recommended for psychosis, as an adjunctive therapy to medication (6). CBTp is a trauma-'informed' therapy, in that it involves making sense of how trauma has shaped a person's difficulties, and learning strategies for managing trauma-related distress (7, 8). However, it does not focus directly on the key psychological mechanism in the development and maintenance of PTSD – vivid, sensory trauma memories that are poorly contextualised in autobiographical memory (4, 9, 10). Trauma-Focused CBT (TF-CBT) is recommended for PTSD (11), which includes 'trauma memory reprocessing', i.e., targeting trauma memories directly, through imaginal exposure, in vivo exposure, and experiential and cognitive techniques to modify their associated meanings. These techniques elaborate and contextualise trauma memories in autobiographical memory so that they become less distressing and less likely to intrude involuntarily (e.g. as flashbacks or nightmares). However, therapists are reluctant to address PTSD symptoms directly in people with psychosis as they fear the memory reprocessing procedures may exacerbate psychotic symptoms (12). These concerns have excluded people displaying psychotic symptoms from all prominent PTSD trials (13).

Three recent systematic reviews (14-16) have all concluded there is emerging evidence from open and pilot Randomised Controlled Trials (RCTs) (17-19) and case-series studies (20-24) that treating PTSD can be safe and efficacious in psychosis. The largest RCT was carried out in The Netherlands (19), and recruited adults with psychosis and meeting full diagnostic criteria for PTSD. Compared to the waiting list group, trauma focused therapies led to improvements in PTSD symptoms with large effect sizes (ES) (0.78; $p<0.001$, in the Prolonged Exposure (PE) arm; 0.65; $p=0.001$, in the Eye Movement Desensitization and Reprocessing (EMDR) arm) as assessed with a continuous measure of PTSD symptoms (Clinician-Administered PTSD Scale (CAPS) (25)). Furthermore, 57% in the PE group (N=53), the type of therapy most similar to the one being evaluated in the current trial, achieved a loss of PTSD diagnosis, compared to 28% of the waiting list group (N=47). End of therapy effects were maintained at both 6m (26) and 12m (27) follow-up time points, with similar results obtained on secondary outcomes.

There have been three recent UK studies (one RCT and two case-series studies) in this area (20, 21, 28). Steel and colleagues (28) also showed that psychological therapy was safe and feasible in a small RCT with people diagnosed with schizophrenia-spectrum

disorders (N=61). However, no difference was found between therapy and Treatment-As-Usual (TAU) groups on PTSD symptoms on the CAPS-S (CAPS for Schizophrenia; (29) either at the 6m (end of therapy; ES=0.26; p=0.39) or 12m (ES=0.29; p=0.39) follow-up time points, with both groups improving. There are two potential reasons for the discrepant results between the UK and Dutch trials. First, the therapy protocol in the Steel et al trial involved cognitive restructuring only, without the exposure element, unlike the Dutch study. Second, participants did not meet full PTSD diagnostic criteria in the UK trial. As a result, participants presented with less severe, and potentially less stable, PTSD symptoms compared to other trials, potentially leading to some degree of spontaneous recovery occurring in both arms.

We will address these limitations in two ways. First, our proposed intervention, TF-CBTp, includes trauma memory exposure, which is hypothesized to be central to effective trauma-focused therapy for PTSD (30). This standard PTSD therapy will be integrated with the standard therapy for psychosis, CBTp, according to our previous theoretical models(3, 31, 32), practice recommendations (8) and case-series of TF-CBTp (20-22). Second, all participants will meet PTSD diagnostic criteria and will be screened for the presence of at least one re-experiencing symptom (33, 34), to ensure specificity of presenting symptoms to PTSD (35), and on which to anchor the trauma reprocessing therapeutic procedures. The diagnostic interview will put particular emphasis on assessing symptom stability i.e., continuous presence of symptoms, attributable to the index trauma, for 1m minimum, as specified in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5 (36)).

Integrating TF therapy with CBTp means that it is more intensive and lengthier than the PE intervention reported by the Dutch group (nine months compared to eight weekly 90-minutes sessions over 10 weeks, respectively). However, van den Berg and colleagues have since reported their protocol had too few sessions, and have recommended longer therapy (37). Psychosis and PTSD symptoms are often intertwined (3, 4), for example hearing the voice of an abuser, experiencing physical sensations of being interfered with, or visions of past torturers (i.e., auditory, somatic, and visual hallucinations); or believing past abusers implanted a chip in your brain to track you (paranoid delusions). In practice it therefore makes little clinical sense to treat the PTSD and psychosis symptoms separately. NICE (6) recommend a minimum of 16 sessions over 6m or longer for psychosis, with more sessions leading to better outcomes (38). Therapy lasting 12m plus boosters is recommended for complex PTSD where there are multiple or chronic traumas (39), which is the case for most of the people with psychosis seen in services. Therefore, TF-CBTp is shorter and potentially less costly than if the two conditions were addressed separately. In general, integration of exposure procedures within standard therapies is preferable for complex, co-morbid populations (40, 41).

To conclude, the current evidence derives from a range of diverse small trials in different health settings. They clearly demonstrate feasibility and promise of useful effects, but a definitive, pragmatic effectiveness trial is now needed. The National Institute for Health and Care Excellence (NICE) have recommended that "*an adequately powered, multi-centre RCT is needed to test whether a CBT-based trauma reprocessing intervention can reduce PTSD symptoms and related distress in people with psychosis and schizophrenia*" (6). The recent Cochrane Review (14) also recommended that good quality evidence is required on trauma-focused therapy in psychosis individuals with co-morbid PTSD. This

study follows these recommendations and will provide a definitive test of whether TF-CBTp is safe, and clinically and cost-effective in people with psychosis.

Objectives {7}

Our research question is the following: Is TF-CBTp in addition to TAU clinically and cost-effective in reducing post-traumatic stress symptoms in people with PTSD and psychosis at the end of therapy, compared to TAU alone?

Primary aim: To evaluate the effectiveness of a manualized trauma-focused therapy for psychosis (TF-CBTp) on post-traumatic stress symptoms in people with current PTSD and psychosis at the end of therapy (9m post-randomisation).

Secondary aims:

1. To compare the two groups at 9m post-randomisation (end of therapy) on: (i) percentage of individuals achieving a loss of PTSD diagnosis, and showing clinically significant change; (ii) PTSD symptom clusters; psychosis symptoms and associated distress; emotional well-being; suicidal ideation; substance use; psychological recovery; social functioning; (iii) cost-effectiveness;
2. To determine whether therapy effects endure 24m post randomisation (15m post end of therapy), including both clinical and cost-effectiveness;
3. To determine the acceptability of TF-CBTp in participants and therapists;

Trial design {8}

The STAR (**S**tudy of **T**rauma **A**nd **R**ecovery) trial is a rater-blind, parallel arm RCT comparing an integrated therapy to address post-traumatic stress and psychosis symptoms (TF-CBTp) in addition to TAU to TAU alone, in individuals with co-morbid PTSD and psychosis across five sites. Randomisation will be in the ratio 1:1 to the two groups and will be stratified by centre. It will be a definitive, pragmatic clinical and cost-effectiveness superiority trial lasting four years and six months (54m). The Consolidated Standards of Reporting Trials (CONSORT) diagram showing the design, participant flow, and assessment timepoints is provided in Appendix 1.

An internal pilot study will ensure the integrity of trial recruitment; protocol safety and adherence; and outcome data (42). The internal pilot will last 16m following the start of recruitment and will include checks for these categories, at 6m, 12m and 16m post recruitment start. The preliminary stop/refine/go criteria (see Appendix 2) will be reviewed with the DMEC, TSC and funder during the study.

Methods: Participants, interventions and outcomes

Study setting {9}

There will be five recruiting sites across England (South London and Maudsley (SLaM); Greater Manchester Mental Health; Cumbria, Northumberland, Tyne and Wear; Oxford Health; Sussex Partnership), all of which are Foundation NHS mental health Trusts and have close links with Higher Education Institutions (HEIs) (King's College London (KCL); University of Manchester; Newcastle University; Oxford University; University of Sussex). Back-up sites (e.g., Berkshire Healthcare; Tees, Esk and Wear Valleys; Lancashire and South Cumbria NHS Foundation Trusts) are available in case of unforeseeable problems in any of the sites.

The five NHS Trusts serve an ethnically diverse population and provide mental health care across a range of services in a variety of settings, for instance adult community mental health teams (CMHTs) and primary community mental health teams (PCMHTs), Community Treatment teams, Psychiatric Liaison teams, Assessment and Liaison (A&L) and Assessment and Treatment (AT) services, Early Intervention for Psychosis (EIP) services, recovery teams, outreach teams, home treatment teams, residential units, inpatient wards, outpatient clinics, specialist services, allied third sector services.

Eligibility criteria {10}

The target population will be adult mental health patients in secondary or tertiary care presenting with current distressing psychotic and PTSD symptoms, meeting diagnostic criteria for PTSD and schizophrenia-spectrum diagnoses (SSD). The latter will be determined by the research team following clinical notes review and consultation with care team, as appropriate, and the former by diagnostic assessment using a standardized measure.

Potential participants with SSD who report a past index trauma, defined as event(s) experienced at least 1m ago and still affecting them now (ascertained using the Mini-Trauma And Life Events (TALE) checklist (5 items depicting common traumas + 1 item in two parts ("do any of the event(s) reported still affect you now and if so which one(s) currently affect you most") (43)), will first be screened for the presence of at least one of the five re-experiencing items from the PTSD Checklist for DSM-5 (PCL-5; (34), to ensure participants are presenting with PTSD-specific symptoms on which to anchor the trauma-focused therapy. Participants who satisfy the re-experiencing symptom criterion will then be administered the full length TALE checklist (44), to determine trauma nature and timing, and elicit any other index traumatic event(s). They will then undergo a PTSD diagnostic interview based on the identified index trauma(s), according to the DSM-5 (36) criteria, to ensure presence and stability of PTSD symptom criteria.

People with SSD do not necessarily experience continuous psychotic symptoms, such as delusions and hallucinations, which typically are the targets of psychological therapies: their symptoms may have remitted, or they may present with cognitive or functional impairments only. We will therefore have the additional requirement that individuals report current distressing hallucinations and/or delusions (over the past month), as specified by previous CBTp trials (45, 46).

These specifications will ensure inclusion of people with at least moderately severe and stable PTSD and psychotic symptoms. Traumatic events can occur before or after

psychosis onset, and co-morbid PTSD presentations are present in all stages of psychosis presentations. We will therefore not place any restrictions on type or timing of traumatic exposure, or participants' age (apart from those applied to adult services).

Inclusion/Exclusion Criteria

Inclusion: Potential participants must meet the following criteria to be eligible:

(i) Presence of SSD (F20-29 diagnoses; International Statistical Classification of Diseases and Related Health Problems, 10th Edition; (ICD-10; (47)) from clinical notes review, if necessary supplemented by information from the care team.
(ii) Scoring 2 or above ('moderate' intensity) on the intensity of distress item of the Delusions and/or Hallucinations Psychosis Symptom Rating Scales (PSYRATS (48)), adapted to include hallucinations in all modalities;
(iii) Reporting past trauma(s), occurring at least 1m prior to assessment, including those related to psychotic breakdown or its treatment (49), assessed using the mini-TALE and TALE Checklists (43,44);
(iv) Reporting still being currently affected by at least one traumatic event, assessed using the mini-TALE and TALE Checklists (43,44);
(v) Scoring 2 or above ('moderately') on one of the five re-experiencing items from the PCL-5 (34)
(vi) Meet DSM-5 (36) symptom criteria for PTSD diagnosis, assessed using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5 (50)), which includes the criteria of 1m stability of symptoms and demonstrable link between the index trauma event(s) and presenting symptoms;
(vii) Both individuals on antipsychotic treatment, and those who decline to take medication, will be included, as long as no major medication changes have occurred in previous 3m (i.e., having started or stopped antipsychotic medication, or a switch to or from Clozapine);
(viii) Aged 18 and above;
(ix) Able and willing to engage in psychological therapy and consent to study procedures.

Exclusion:

(i) Current, primary diagnosis of substance use disorder;
(ii) Organic factors implicated in the primary aetiology of psychosis and/or PTSD;
(iii) Current (or in previous 3m) engagement in trauma-focused therapy (i.e., any therapy that focuses on reprocessing trauma memories; therapies such as CBTp would be operationalised as 'trauma-informed' rather than 'trauma-focused', since they may include past traumatic experiences in the developmental formulation, but would not include memory work);
(iv) Insufficient English to provide informed consent or complete assessments without the help of an interpreter;
(v) Currently experiencing an acute mental health crisis.

Who will take informed consent? {26a}

A summary of the identification and consenting of participants is provided in Appendix 3. Because of the sensitive nature of the questions for determining eligibility, we will ensure that fully informed consent is obtained prior to eligibility assessments. Our specific procedures will be dictated by local NHS Trust consent procedures but will adhere fully to the principles outlined below.

Participants will be given the opportunity to discuss the study with the Research Worker (RW) prior to giving written informed consent, and they will be offered at least 24 hours to consider their participation in the trial. Potential participants known to have a carer or family will be provided with a Carer Information Sheet, in addition to the usual Participant Information Sheet, to increase carer and family involvement in supporting individuals with the consent process. The RWs will assess risk and capacity to provide consent throughout the identification and assessment procedures, with input from the Trial Coordinators and/or Site Leads, who are all trained clinicians, if necessary. The limits of confidentiality will be made clear to participants from the outset (see confidentiality section). We will have a standard protocol for assessing and managing safeguarding and risk disclosures, which will follow safeguarding policies and risk assessment procedures of the local NHS Trusts.

Unless people have previously provided written consent to be contacted, or contact the research team independently (see additional recruitment sources in Recruitment section), potentially eligible participants will first be approached by clinical teams responsible for their care to ascertain interest in being contacted about the study, and will be provided with a study leaflet with a summary of the research. If interested they will be invited by the clinical team to either contact the research team directly, or to give their permission to be contacted to learn more about the study. The research team will then contact the potential participant and obtain consent to review their clinical notes to make an initial eligibility check and to determine/manage current risk. The potential participant will be provided with the Participant Information Sheets at this stage.

If initially eligible, potential participants will then be invited by the RW for a face to face meeting to be provided with further information about the study, including a recruitment video, to clarify any questions and to provide written informed consent to complete eligibility assessments and to participate in the study. The research team will not invite a potential participant without the responsible clinician or healthcare professional having indicated that it is appropriate to do so; i.e. that they meet study criteria and there are no clinical contra−indications.

Individuals who do not provide consent to participate (or who are assessed as unable to consent), and those who are determined not to be eligible at either the initial or full eligibility assessment stage, will be provided with written information on local support services. For those who are determined not eligible at the full assessment stage, a copy of the trauma assessment will be provided to the team, with the person’s permission, in line with current best practice guidelines stipulating that trauma histories should be routinely assessed in people with psychosis (51, 52).

Eligible participants will then be invited to complete the baseline assessment. It will be made clear to participants that they have the right to withdraw from the study at any time for any reason, without the need to justify their decision, and that it will not affect their routine care. The investigator also has the right to withdraw participants from the study in the event of clinical contra-indications. Should a participant withdraw from therapy only but not from the study, efforts will be made to continue to obtain follow-up data, with the permission of the participant. Should a participant withdraw from the study, we will still use any previous data collected from that participant up to the point of withdrawal, but will make no further attempt to contact or collect data, as specified by the UKCRC CTU network guidance.

Written informed consent will be documented on the consent form, with both a participant and RW signature. The original copy of the consent form will be retained in the investigator site file. Copies of the consent form will be scanned into the participant's clinical records and a hard copy given to the participant for their own personal records. The RWs who will be responsible for taking written informed consent will have received mandatory training in Good Clinical Practice (GCP) alongside internal additional training by the study team. Throughout the recruitment and research process all efforts will be made to tailor to participants' needs and preferences.

Due to the COVID-19 pandemic, adaptations to the procedures outlined above (relating to taking informed consent, conducting eligibility assessments and conducting baseline assessments) and will be required. These are outlined in detail in appendix 6 (specifically please see sections 6.3 and 6.4).

Participant and Carer Information Sheets for the trial randomisation and qualitative interviews (see below) were developed in line with requirements set out in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6 (R2); (53)) guideline for GCP and the sponsors' Standard Operating Procedure for Informed Consent. Extensive Patient and Public Involvement (PPI) input was obtained to ensure appropriate wording and accessible formatting.

Additional consent provisions for collection and use of participant data {26b}

All trial participants will be asked whether they would be willing to be contacted at a later stage for participating in further studies related to the trial. This consent to contact will include the qualitative interview regarding the acceptability of the intervention, should they be randomised to the intervention group. It will be made clear that this is optional and that declining consent to be contacted for participation in additional studies will not prevent them from taking part in the trial.

For the qualitative interview, it will also be made clear that not everyone will be contacted, since we will only be recruiting a sub-sample. If they indicate willingness, an expert-by-experience researcher with psychosis will contact them directly once they have completed the intervention (including people who choose to end therapy prematurely). Consent procedures will be as above. Therapists will also provide written informed consent to participate in the interview, according to the same principles outlined above.

Interventions

Explanation for the choice of comparators {6b}

The comparator will be TAU, which consists of multi-disciplinary psychologically-informed care, delivered by mental health services.

Specifically, TAU will include standard psychiatric care consisting of medication and outpatient psychiatric appointments; psychologically-informed case-management, including regular meetings with a care coordinator; access to a range of supportive psychotherapies. Clinicians involved in participants' treatment will receive a manual summarising current best practice and evidence-based treatment guidelines to promote standardisation of good quality TAU.

Intervention description {11a}

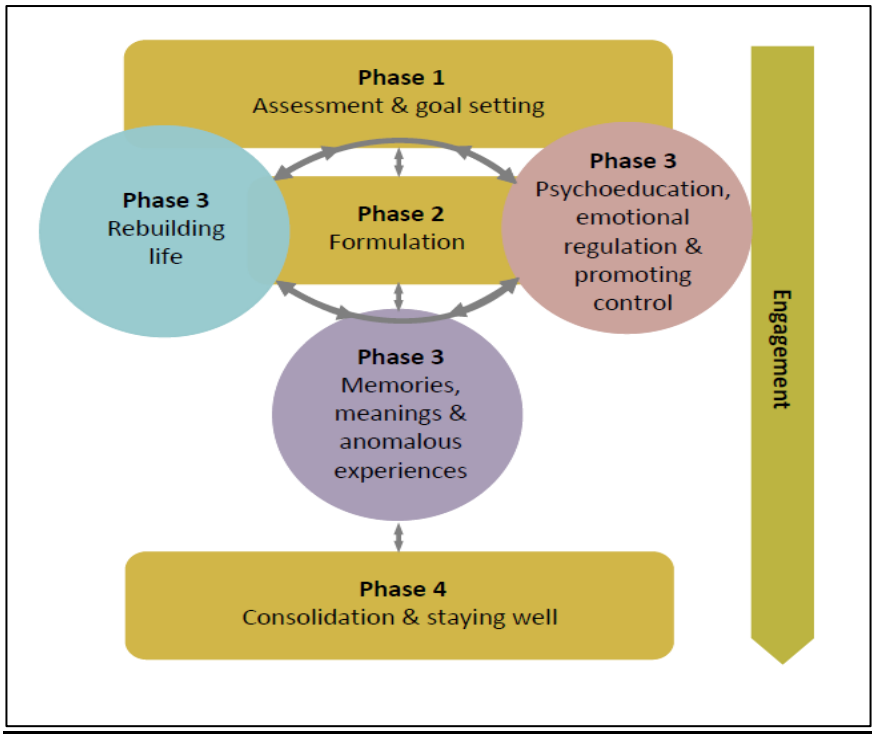
Trauma-Focused Cognitive Behaviour Therapy for psychosis (TF-CBTp): TF-CBTp is a manualised therapy integrating standard psychological therapy for PTSD and for psychosis (3, 8, 20, 21, 22, 23, 24, 31, 32). It will be delivered over a period of 9m. Approximately 26 weekly or bi-weekly individual, face to face, 60-90 minutes sessions, will be offered in the first 6m. Bi-weekly rather than weekly sessions have a potential to be beneficial during the trauma reprocessing phase of the therapy (54, 55) but it will be left to client choice. A further 3 monthly sessions will be offered during the next 3m, following the recommendations made by NICE (6). They will be done jointly with the care coordinator, if possible, to assist with generalisability of therapy effects. Therapists will liaise with clinical teams throughout the delivery of therapy to discuss progress, with the participant's consent, and to share any potential risk to self or others.

Due to the COVID-19 pandemic, adaptations to the procedures outlined above relating to intervention delivery will be required. These are outlined in detail appendix 6 (specifically please see section 6.5).

TF-CBTp is formulation-based and individualised to tailor to the specific needs of the individual, depending on the type of presenting post-traumatic stress symptom (for example, re-experiencing, avoidance, negative cognitions and mood, hyperarousal, dissociation) and type of psychotic symptom (for example, hallucinations or delusions). Therapy is conducted in a flexible style with an emphasis on engagement and building a good therapeutic relationship, which is key throughout the delivery of therapy. Trauma-focused work can be powerful but also challenging, and throughout a balance is struck between ensuring the person is able to manage distress and improve their coping if necessary, whilst not delaying or avoiding the trauma-focused interventions. Overall TF-CBTp consists of four broad, flexible phases: (1) assessment, psychoeducation and goal setting; (2) developing a shared understanding of current difficulties and maintenance cycles i.e., formulation; (3) formulation-driven model-based interventions, consisting of addressing a) trauma memories, anomalous experiences and associated meanings; b) promoting control and c) rebuilding your life, with cognitive, behavioural and interpersonal emotional regulation strategies integrated as necessary into model-based interventions; and (4) consolidation and staying well (See Figure 1). Phase 3 crucially includes the memory reprocessing strategies, which are hypothesised to be necessary for the reduction of post-traumatic stress symptoms. The aim here is to reduce re-experiencing and/or associated psychotic symptoms through elaboration of the trauma memory and discrimination of triggers. The method of elaboration will be determined by the nature of the person's memory intrusions as specified in the formulation but will include established reprocessing strategies such as imaginal reliving and imagery rescripting.

Given the time limited nature of the therapy, and that the main target of therapy is post-traumatic stress symptoms, the aim is to adhere to PTSD model-based interventions unless adaptations for psychosis are necessary. In practice therapy is formulation based and hence personalized and pragmatic in that it is adapted to the individual, with clinicians able to shift focus according to clinical need. Similarly, therapy speed and progression are tailored to the individual. Psychosis focused interventions are embedded throughout to address psychosis-related experiences, appraisals, and behaviours as they arise.

Figure 1: Trauma-Focused Cognitive Behaviour Therapy for psychosis (TF-CBTp) overview



Criteria for discontinuing or modifying allocated interventions {11b}

There are no trial criteria for discontinuing or modifying allocated interventions at the individual participant level. It will be made clear to each participant that, should they find any aspect of the research distressing, and/or no longer wish to continue with either the research or the therapy, they will be able to withdraw from either or both without having to give a reason or this impacting on their usual clinical care in any way. Nevertheless we will invite a sub-section of people who choose to end therapy prematurely to participate in the qualitative interviews so that they are given an opportunity to feedback on their reasons for doing so if they wish to, and to help us identify barriers and potential solutions to engagement in therapy. The feedback from qualitative interviews will inform the therapy manual throughout the intervention phase.Clinical teams will be responsible for the provision of TAU interventions, with no interference from the research team.

At the trial level, it is an important subsidiary goal of the trial to establish the safety of the intervention, and we will take all appropriate steps during the conduct of the trial for ensuring participant safety, in both arms of the trial. Concerns over safety of TF-CBTp, identified through Adverse Events (AEs) and Serious Adverse Events (SAEs), therapy sessional ratings or qualitative interviews, would, in the first instance, lead to therapy protocol amendments, but could lead to study termination at any time. Our experience with

this population and type of therapy suggests that the therapy proving unacceptable or too distressing to participants is a low risk. However, we would see this unlikely eventuality as an important outcome of the study, as it would provide empirical evidence to inform future studies on what should be avoided in people with PTSD and psychosis, rather than relying solely on clinical intuition.

Should the therapy prove aversive or too distressing to a significant minority of participants, we would consider an elective stop to the study. However, this was not a concern in the pilot studies and we think this unlikely. We also have the oversight of the Data Monitoring & Ethics Committee (DMEC) committee who will be reviewing trial progress and the occurrence of SAEs. So far the evidence suggests the opposite, with van den Berg and colleagues (56) showing that fewer SAEs, symptom exacerbations and revictimization experiences were reported in the therapy groups, compared to the Waiting List group, suggesting that therapy decreases risk.

The trial may be prematurely discontinued by the NIHR based on new safety information or for other reasons given by the DMEC/Trial Steering Committee (TSC); the latter can recommend discontinuing the study. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

Strategies to improve adherence to interventions {11c}

The intervention will be delivered by trained psychological therapists with experience of working with severe mental health problems, to ensure competence in engaging this complex population. They will receive training in delivering TF-CBTp by the study team (three days training, with two-day booster sessions in subsequent years). Therapists will travel to participants' team base or home/residence if required, to maximise retention in the therapy.

Four related aspects will be monitored and assessed: (i) participants' adherence to the therapy; (ii) therapist competence (iii) therapist adherence to the manual (iv) overall therapy fidelity.

Participants' adherence to the therapy will be assessed by recording the number of sessions offered and attended, including length of sessions attended, and completion of between-sessions tasks (therapy 'homeworks').

Therapist competence and adherence to the manual will be monitored through recordings of therapy sessions, with participants' consent. This is a widely accepted approach to the standardisation of psychological therapies. Therapists will have weekly supervision from a senior clinical psychologist on each site, who will listen to and provide detailed feedback on a selection of therapy tapes, with participants' consent, on a weekly basis, to ensure competence and adherence. All therapists and site supervisors will also meet remotely with the research team therapy leads for monthly group supervision. This will be done throughout the therapy delivery period to provide quality assurance and ensure action can be taken if required.

Therapy tapes from five participants on each site (total of 25 participants) will be randomly chosen, with participants' consent, to be rated by a clinician independent from the trial, to provide an objective verification of therapist competence and adherence to the manual.

Six random tapes per participant, stratified by stage of therapy (with at least three tapes from Phase 3 where the formulation-driven model-based interventions occur) will be rated (total of 150 tapes).

Therapist competence will be rated by amalgamating relevant items from 3 existing measures assessing skills and competences related to basic CBT (57); psychosis work (58); and PTSD trauma-focused work (PTSD-adapted version of the Cognitive Therapy Scale – Revised (CTS-R) (59), available at oxcadatresources.com). A rating form for therapist adherence to the manual will be designed specifically for the study, and will consist of a list of therapeutic procedures extracted from the protocol.

To assess overall therapy fidelity, following each session, therapists will complete a checklist to record content of sessions in terms of agenda targets, homework tasks and change strategies used. These data will be extracted at regular time points throughout the trial to check therapy milestones are being met and ensure the therapy protocol is being followed. This ongoing monitoring will pick up on any fidelity issues across sites or individual therapists and will inform training and supervision content.

Relevant concomitant care permitted or prohibited during the trial {11d}

It would be unethical to restrict the therapeutic options of the clinical teams participating, and we will not be asking referrers to withhold any treatment or interfere with decisions to discharge to primary care or other care pathways, in either group. It is unlikely that trauma-focused psychological therapies will be available; nevertheless, we have added current engagement in trauma-focused individual psychological therapy at the time of, or up to 3m prior to, randomisation as an exclusion criterion. All routine or additional treatments (including medication changes) in both conditions will be monitored as part of the service-use data collection.

Provisions for post-trial care {30}

The TF-CBTp intervention includes monthly sessions in the final 3m of the therapy, to be done jointly with the care coordinator, if possible, to assist with generalisability of therapy effects and planning of future care. Therapists will liaise with the clinical teams throughout the delivery of therapy to discuss progress, with the participant's consent, and to share any potential risk to self or others. A therapy outcome report will be written by the therapist to the clinical team, with participants' consent and shared with the participant, documenting progress made and recommendations for future maintenance of therapeutic gains. The therapist and/or study team, which involves experienced clinicians, will be available to contact by participants' clinical teams, should they wish, following participants' discharge from therapy.

In the event that participants are harmed during the research they may have grounds for legal action for compensation against King's College London and/or SLaM NHS Foundation Trust, but they may have to pay their legal costs. The normal National Health Service complaints mechanisms will be available to participants (if appropriate). King's College London has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, and participants may be entitled to make a claim for this.

Outcomes {12}

We will assess PTSD symptoms as our primary outcome at the end of therapy. PTSD symptoms in the past month will be assessed on the CAPS-5 (50), a semi-structured interview assessing the severity of symptoms delineated in DSM-5 (36). It is currently the recommended clinical interview in PTSD research, including in psychosis populations (19). The total symptom severity score will be the specific measurement variable.

Our secondary outcomes will consist of a range of clinical domains it is anticipated the therapy may impact on, namely percentage of participants achieving loss of PTSD diagnosis and demonstrating clinically significant and reliable change; self-reported PTSD symptoms; psychosis symptoms; emotional well-being, suicidal ideation and substance use; psychological recovery; and social functioning. Total or sub-scale scores for each questionnaire will be the measurement variable. See Data Collection section for a full list of measures.

We will collect further information on participants and their trauma experiences to characterise the sample, namely: demographic variables (age; gender; ethnicity; migrant and asylum status; relationship status; education; living situation; working status); clinical variables (age at start of psychotic symptoms and at first contact with mental health services; number of past psychiatric admissions; psychotropic medications); trauma nature and timing (single vs polyvictimisation; childhood vs adulthood; interpersonal vs non-interpersonal; psychosis-related vs non-psychosis-related).

In line with the recent CONSORT - Social and Psychological Interventions (CONSORT-SPI) (60) guidance, which recommends minimising the distinction between primary and secondary outcomes, all outcomes will be reported at all assessment time-points.

In relation to cost-effectiveness, we will collect data on service use, medication use and health related quality of life at all assessment time-points. In addition, service use will be assessed for the previous three months at the ‘keeping in touch’ phone calls between the end of therapy and final follow-up, to maximise the accuracy of these data. Outcomes will be expressed in terms of Quality Adjusted Life Years (QALYs) and costs. See Economic Analysis section for further details.

Acceptability of the therapy, through qualitative interviews, will also be assessed as a secondary outcome in the therapy group. This will occur once participants have concluded or chosen to end therapy.

Additional studies are planned that will investigate mechanisms potentially mediating the relationship between the intervention and outcomes. These studies will complement the objectives of the trial, examining how we can enhance the effectiveness of psychological therapies for psychosis by identifying specific psychological and neural targets for therapeutic intervention. These studies will not require additional participants nor disrupt their clinical care. Amendments detailing these additional studies will be submitted for ethical approval as and when required.

Participant timeline {13}

See Appendix 4 for Schedule of enrolment, interventions, and assessments.

Independent assessors (RWs) blind to study group will conduct all eligibility and research assessments. Following providing written informed consent to participate and completing

the baseline assessment, eligible participants will be randomised within two working days. They will be contacted with the outcome of the randomisation within a week by the therapist, and offered a first therapy session within the following week, whenever possible. Therapy will last 9m in the intervention group. Participants will remain enrolled in the study for two years in total.

Following written informed consent, the eligibility assessment will be administered in a set order, starting with the shortest measures. Anyone not meeting inclusion criteria on a scale will not proceed to the remaining measures, to minimize participant burden. It is anticipated that eligibility assessments will last between 15 minutes and one hour, depending on eligibility of the potential participant. No honorarium will be provided for eligibility assessments, but people who are not eligible will be provided with information on local support services, and will have any travel expenses remunerated.

Research assessments to assess PTSD and secondary outcomes, including cost-effectiveness outcomes, will take place at four time points (baseline, 4m (mid-therapy), 9m (end of therapy; primary endpoint), and 24m (15m post-therapy) post-randomisation), and there will be four 'keeping in touch' phone calls where service use will be briefly assessed and contact details updated (at 12m; 15m; 18m; and 21m, post-randomisation). The 24m post-randomisation assessment will enable us to determine whether therapy effects endure on both our primary and secondary outcomes. The 4m assessment and the phone calls will also help retention into the trial and reduce loss to follow-up, by avoiding having lengthy periods of time in the study without contact from the research team. A brief questionnaire will be offered to participants to complete anonymously following the baseline and 24m follow up assessments to gather feedback on their experience of the research assessments and overall study respectively.

Assessments will be conducted at locations convenient for the participant (at either NHS, University or residential locations). It is anticipated that assessments will last between 2-2.5 hours, including breaks. Participants will receive a reimbursement (for their time) of £20 for completing each research assessment, plus travel expenses. Participants will be offered choices regarding length of assessments, including the option of breaks and multiple testing sessions. Assessment measures will be clearly prioritised so that the most important will be collected first to avoid missing data. 'Keeping in touch' phone calls are likely to last approximately 15 minutes and will not be remunerated.

Due to the COVID-19 pandemic, adaptations to the procedures outlined above relating to conducting the research assessments will be required. These are outlined in detail in appendix 6 (specifically please see section 6.4).

A sub-sample of participants in the TF-CBTp group (N=35; 7 per site), who give their consent, will be consecutively recruited across all sites in the study to take part in a qualitative interview. This interview will ask them for feedback on the therapy, to explore acceptibility and satisfaction with the therapy they received. Close attention will be paid to any emotional distress resulting from trauma reprocessing procedures, in particular potential impact on psychotic symptoms, and whether this was considered unacceptable or unnecessary. Interviews will be conducted by a service user researcher with support from the research team in each site. It is anticipated that interviews will last approximately one hour, and participants will receive a reimbursement (for their time) of £10, plus travel expenses.

Sample size {14}

To account for the partially nested design, calculations were performed using -clsampsi- in Stata. We account for: clustering in therapy arm with Intra-Class Correlation (ICC)=0.01 with 10 therapists over the trial period (conservative; e.g. Steel et al (28) had 13 therapists) each with an average of 12 participants and variation in the cluster size of 12; no clustering in TAU group; 1:1 allocation; 0.05 significance level; baseline-endpoint correlation of 0.5 (range in previous data (19, 28): 0.4 - 0.7) reducing the standard deviation (SD) to 0.866 from a standardised value of 1.

For an effect size of 0.4, 120 people per group in the analysis set has 91% power. As a sensitivity check, with 240 participants in the analysis set, if the ICC=0.05 we would still retain 85% power. Alternatively, if the ICC=0.01, 240 participants has 80% power to detect an effect size of 0.33. To account for a conservative 20% attrition to primary endpoint, we will recruit 300 participants into the study (60 per site).

In the Dutch pilot trial (19), using an earlier version of the outcome measure to be used in the current study (CAPS-5 (50)), the observed SD was 16. A clinically relevant within-person change on the CAPS-5 scale is considered to be 15 points. The observed improvement in TAU group at the end of therapy was 9 points, which we use to derive a between-group difference of 6 points. In the UK trial (28) a slightly modified version of the CAPS (CAPS-S; (29) was used. There was an improvement in TAU group of 17 points at post-therapy (therapy lasted 6m in that study, compared to 10 weeks in the Dutch trial) and had a pooled standard deviation of 24.45, indicating greater variability in the modified measure but qualitatively similar pattern to the descriptive statistics. Therefore a 6 point between-group difference on the CAPS-5 measure would mean an average within-person change in the TF-CBTp group of more than 15, which is clinically meaningful, and corresponds to a between-group effect size of 0.375.

Previous trials with similar complex psychosis individuals have shown excellent retention: the follow-up rate in a trial for CBT for command hallucinations trial (61) was 83% at the 18m post-randomisation follow-up, with 93% providing outcome data at either the 9m or 18m time points; for the FOCUS trial (with Clozapine-resistant individuals (62)) it was 89% and 92% at the 21m and 9m follow-up time points, respectively. The trial by Steel et al (28), with the same population as this study, had 15% loss to all follow-up, albeit with a shorter timescale (6m and 12m post-randomisation). We have therefore assumed 80% retention in the trial to be on the conservative side.

Based on our previous experience of recruiting for similar trials on the five sites, and based on Steel et al (28), we anticipate we will need to screen 1,200 people to recruit 300 participants, with 75% of screened individuals not being eligible: 50% will not meet PTSD or SSD or psychosis symptoms criteria; 18% will meet other exclusion criteria; 2% will be currently receiving trauma-focused therapy; 5% will withdraw before completion of assessments. We anticipate 60 people per month will provide consent to be screened for eligibility, leading to a recruitment rate of 15 people per month (3 per site; 1.5 average in the first 4m).

For the qualitative study, a nested qualitative approach will be employed with participants (N=35; 7 per site) and therapists (N=5-10; 1-2 per site, depending on number of therapists employed per site) to identify key aspects of acceptability and tolerability in receiving and

implementing the therapy that could not be detected by quantitative measures alone. At least five participants (one per site) who chose to end therapy prematurely will be included in the interviews.

Recruitment {15}

Our combined five Trusts treat around 36,000 psychosis patients. It is anticipated 15% will meet PTSD diagnosis (2), meaning there will be a pool of approximately 5,400 people potentially eligible. Our anticipated screen target is 1,200 i.e., 22% of the pool of potentially eligible participants.

All sites have highly successful records of running psychological therapy trials with psychosis individuals, and of recruiting and retaining skilled CBTp therapists. All have access to Clinical Research Network (CRN) facilities to assist with recruitment and blind breaks. Back-up sites are available in case of unforeseeable problems in any of the sites.

The research team will liaise with the staff in key NHS services through presentations, regular attendance at clinical team meetings and email/phone to identify potential participants. Recruitment will occur in all services providing mental health care across the five NHS Trusts, to ensure as wide a range of ages and clinical presentations as possible.

Additional sources of recruitment will include:
1) Recruitment databases or consent for contact initiatives e.g. SLaM's Consent for Contact (C4C) provides access to existing research recruitment databases, using Clinical Record Interactive Search (CRIS), an IT system that anonymises and provides authorised researchers with access to SLaM's 230,000 electronic health records.

2) Through direct approach: we intend to place recruitment posters and leaflets in the main clinical areas of mental health teams. Posters and leaflets will provide basic details of the study and will invite potential participants to approach the research staff either via their clinical team or directly. Additional self-referrals are also possible as a result of interest generated through media/public engagement events and NHS Trusts' R&D websites or newsletters. Further information will be available on the study website, which may also generate self-referrals. If a potential participant makes a direct contact to the research team, they will be asked for consent for us to approach their clinical team and access their basic personal information to make an initial suitability check, following the same procedures detailed in the consent section above.

We will have a small amount of promotional merchandise to help with recruitment, for example pens, mugs, and stress balls with the trial logo. We will distribute merchandise with trial logos to clinicians to help remind them to refer to the trial, and to consented participants to remind them of their involvement in the trial. A Twitter page for the trial will be created to help liaise with clinicians and individuals with lived experience interested in the trial.

Recruiting below target is the most significant risk to the study. If recruitment is below 80% at 6m following the start of recruitment, we will: (1) enlist further help from local CRNs; (2) if recruitment across sites is uneven we will readjust targets so that they are increased at sites showing good recruitment, and lowered at struggling sites; (3) seek R&D permission to add neighbouring Trusts as Patient Identification Centres (PIC) sites, which we have

done successfully in a number of previous trials i.e. neighbouring NHS organisations that identify potential research participants for a research study (e.g. through search of patient databases) but have no other involvement in the research. In line with IRAS guidance, no research activities beyond identifying potential participants will take place at these PIC sites; (4) should difficulties at one or more site prove impossible to be overcome, back-up participating sites will be available, which could be involved with the appropriate transfer of resources; (5) As a last resort, we will discuss with the HTA the possibility of amending our inclusion criteria, following analysis of our screenings data.

Assignment of interventions: allocation

Sequence generation {16a}

Randomisation to the two groups will be undertaken using the web-based King's College Clinical Trials Unit (KCTU) randomisation service. Randomisation will be in the ratio 1:1 to the two groups and will be stratified by centre. Randomisation (at the individual level) will be independent and concealed, using dynamically generated permuted blocks of random size.

Concealment mechanism {16b}

The randomization system is web-based and allocation is made known to the PI, the Trial Coordinator (in order to monitor adherence to the randomisation algorithm), and the trial therapists only at the point of randomization, by email. The allocation is dynamically generated and uses randomly varying blocks of sizes not known to the study team so allocation concealment is assured.

Implementation {16c}

The allocation sequence will be generated dynamically by the KCTU. Authorised individuals will be assigned usernames and passwords to log into the system and randomise participants. These individuals may be blind or unblind to group allocation. Randomisation is confirmed via two sets of emails generated by the system. The first set contains the unblinded group allocation and is sent to relevant unblinded individuals in the team. The second set contains no allocation details but is sent to relevant blinded individuals to confirm the participant is enrolled.

The RWs will enroll participants, and KCTU will assign participants to the two groups. The therapists will inform the participants to which group they have been randomised to.

Assignment of interventions: Blinding

Who will be blinded {17a}

The KCTU randomisation system will ensure blinding of the relevant members of the team. Outcome assessors will be blind. Clinicians, therapists and participants will be unblind. Senior statistician will be blind and trial statistician will be partially blind.

Maintaining blindness of the RWs is crucial, and care will be taken within the research team to avoid accidentally unblinding outcome assessors. Any cases of inadvertent unblinding will be discussed in a TMG, and the DMEC and TSC will monitor unblindings by each centre regularly and implement corrective action if necessary.

Extensive procedures will be adopted to ensure blinding of assessors is maintained: strict separation of therapists from RWs; protocols for answering phones, message taking and secretarial support; separate diaries and security for electronic randomisation information; and separate accommodation and storage procedures for all data. Participants and clinical teams will be reminded prior to each assessment timepoint by the research team that they must not inform the RWs of their group allocation. The Trial Coordinator will oversee the maintenance of blinding and will monitor any blinding breaches closely. Where this occurs during the assessment, measures that have been completed unblinded will be repeated by the other RW at the site or CRN support will be sought. If the break in blind occurs subsequent to the assessment, no further assessments or data entry will be carried out by that assessor. Breaks in blinding will be monitored and recorded.

Procedure for unblinding if needed {17b}

This circumstance is not applicable since participants and therapists are already unblinded.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Procedure for assessments:

Independent assessors (RWs) blind to therapy group will conduct all assessments at the four time points and all 'keeping in touch' phone calls. The RWs will be trained in the assessment battery over a three-day training session at the start of the trial, which will include the use of videos and role-plays. Experts by experience will contribute to the training. Training will be repeated each year to accommodate new RWs and provide top-up training, to maintain reliability and avoid assessor drift. RWs will be supervised by experienced research clinical psychologists (site leads and Trial Coordinator).

Data quality:

RWs will be trained to competence on the main interview outcome measures prior to starting any assessments i.e., they will need to have reached >80% agreement with ratings made by the Trial Coordinator on training videos and role-plays during the initial training stage. Once started, assessments will be recorded, with participants' consent, to conduct further inter-rater reliability on the interview measures. Each RW's assessments will be double-rated by the Trial Coordinator, again until >80% agreement has been reached. These procedures will be repeated every four-six months to minimise rater drift. Inter-rater reliability for our primary outcome will be reported from the double ratings made throughout the lifetime of the trial for a minimum of 60 ratings (excluding those used for rating agreement during the initial competency training stage prior to starting the assessments).

Risks and benefits of assessments:

There is a risk of participants experiencing distress from the assessments, since they will be asked about traumatic events from the past and current difficult experiences such as hearing voices. These risks will be minimised through the appointment of RWs who have a psychology background and have experience of working with populations with severe mental health problems. They will receive training in interviewing skills and how to respond sensitively and empathically to any distress that arises. There will be close supervision of RWs throughout the trial (by experienced Research Clinical Psychologists) and regular

review both within the main trial team (at monthly meetings) and at the TSC and DMEC. Whilst there is evidence to suggest that the assessments are tolerable for people with psychosis, it is possible that some participants may find them to be cognitively demanding, or too lengthy. In order to manage this, RWs will make clear to participants from the start that they can withdraw from the study at any point, which will not affect their statutory care. If an individual becomes distressed whilst completing the assessments, they will be reminded that they take a break at any time, that their involvement is voluntary and that they can decline to answer questions or stop the interview altogether. The RWs will be sensitive to monitoring and assessing how participants are finding the assessments and adapt the pace and content accordingly. Participants will be offered choices regarding length of assessments, including the option of breaks and multiple testing sessions, to minimize fatigue or distress.

All measures have been selected or designed with the participant population in mind with extensive PPI input and are considered suitable for people with psychosis to complete. A range of potential measures for each domain of assessment was presented to the Service User Research Group (SURG; Manchester Psychosis Research Unit) (N=7), who made the final selection, based on consideration of content acceptability and burden. We have made sure the short versions of questionnaires have been selected, when available, to minimize burden.

We will have a standard protocol for managing any distress potentially elicited by the completion of measures, which has been developed in collaboration with experts-by-experience. We have used this successfully in several trials, including those investigating trauma-focused therapy for psychosis. This includes offering telephone contact within 48 hours of assessments to check on participant well-being, and a summary of support and crisis numbers.

The research assessments are not designed to have any direct beneficial effect. However, they may have a nonspecific beneficial effect through providing participants with an opportunity to have empathic, warm and normalising conversations about their difficulties and experiences, which may not be discussed in routine clinical care. Participants' experience of the research assessments will be evaluated following the baseline assessment and at the last assessment (24m) using a brief feedback form, to capture any potential negative and positive aspects.

Regarding the qualitative component of the trial, a potential risk is that some participants may find topics discussed in the interviews distressing, especially if they chose to end therapy prematurely, for instance due to an adverse event related to therapy procedures. However, previous trials of trauma-focused therapy for psychosis have indicated that TF therapy is safe and acceptable to participants (28). Therefore, we anticipate adverse reactions or events related to therapy would only be experienced by a small minority of participants, if any. Further, it is anticipated that the qualitative interviews will provide participants with a supportive space in which to discuss any distress associated with trial participation, assisted by a lived experience expert. All experts by experience will be trained in managing interviewer distress, and experienced clinicians will also be available if needed to provide support during interview or follow-up contacts. During qualitative interviews, participants will be reminded at the start and throughout the interview that they are able to take breaks or stop at any point and that they do not have to answer any questions if they wish not to.

Measures:

Primary outcome: PTSD symptoms in the past month will be assessed on the CAPS-5 (50). The CAPS-5 is a semi-structured interview assessing the severity of symptoms delineated in DSM-5 (36).

The CAPS-5 consists of seven criteria (Criteria A to G). Scores are anchored to an index event, which will be elicited using the mini-TALE and TALE checklists (43,44). The index event could be a single trauma experience or multiple, closely related incidents. In this study meeting Criterion A will not be a requirement (i.e., only events including actual or threatened death, serious injury, or sexual violence), as we will include events related to psychosis and its consequences (e.g., involuntary admission or forced restraint), emotional and physical neglect, discrimination and attachment disrupting experiences, as possible index events (49).. PTSD diagnostic status will be determined by an algorithm of minimum scores on specific items from Criteria B to E, and meeting Criteria F and G, according to DSM-5 diagnostic rules.

Once the index event has been ascertained, the severity of symptoms is scored on a 5-point scale ('absent' to 'extreme') on four criteria: (i) Criterion B: Re-experiencing symptoms; (ii) Criterion C: Avoidance symptoms; (iii) Criterion D: Cognitions and mood symptoms; (iv) Criterion E: Arousal and reactivity symptoms. Criteria F and G are scored dichotomously (Yes/No) on whether the duration of the experience is more than 1m, and has caused subjective distress and impairment in functioning, respectively. The total symptom severity score (total of 20 item scores on Criteria B to E) will be the primary outcome.

Secondary outcomes: All measures listed below consist of standardised questionnaires and semi-structured interviews, with demonstrated reliability and validity. Short forms have been included when available, to minimize participant burden. The timescale of assessment will be the past month for all symptom measures, consistent with our primary outcome (apart from substance use, which will be three months). All have been used in previous trials with psychosis populations and were endorsed by our experts-by-experience advisory groups.

Symptoms:

PTSD: (i) Percentage of people who achieve a loss of their PTSD diagnosis, as determined by the CAPS-5 diagnostic status algorithm; (ii) Percentage of people who show a clinically significant improvement and a reliable change in CAPS-5 scores (iii) CAPS-5 individual symptom clusters (severity scores for the individual Criteria B to E); (iv) Self-reported PTSD symptoms and their associated appraisals and responses will be assessed on standardised, commonly used questionnaires: International Trauma Questionnaire (ITQ (63)); 18 items), which includes Complex PTSD items; Brief Version of the Posttraumatic Cognitions Inventory (PTCI-9 (64); 9 items), which measures cognitive appraisals of the trauma and its aftermath; Dissociative Subtype of PTSD Scale (DSPS; 15 items; (65)), which assesses lifetime occurrence and current frequency of three factors of dissociation, namely psychogenic amnesia, derealisation/depersonalisation and loss of awareness.

Psychosis: (i) The Psychosis Symptoms Rating Scales (PSYRATS (48)) is a clinician-administered semi-structured interview, and will be used to assess the multidimensional aspects of delusions and auditory hallucinations (such as distress, preoccupation, and conviction; 11 items for voices, and six items for delusions). PSYRATS is well suited to assess outcome in psychological therapies (66) and has been used in major RCTs (45, 46). PSYRATS items will also be administered for hallucinations in other modalities (i.e., non-verbal auditory, visual, somatic, olfactory, sexual, gustatory and sense of presence(67)), and additional items will be included to assess multi-modality (i.e., whether different types of hallucinations are experienced at the same or different times)(68). Each item is rated by the interviewer on a 5 point nominal scale (0-4); an additional, continuous self-report rating scale will be added to each item, as there is evidence that the nominal scale is not sensitive to change for some of the items (e.g., delusional conviction is rated as a 3 for conviction ratings of 50-99%, and as 4 for 100%, therefore a 50% change in delusional conviction only incurs a 1-point difference). Both ratings (total scores for each PSYRATs scale) will be reported as secondary outcomes. (ii) Self-reported paranoia (the commonest form of delusions) will be assessed using the Revised Green et al Paranoid Thoughts Scale (GPTS-R; (69); 18 items).

Emotional well-being: (i) Mood will be assessed using the short form of the Depression Anxiety Stress Scales (DASS-21 (70)), which includes 7 items for each of the 3 domains assessed. (ii) Suicidal ideation will be assessed using the Paykel Suicidal Feelings Scale (PSFS; (71); 5 items); (iii) Substance use is highly prevalent in this population, and will be assessed by the Brief Version of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST; (72, 73)) developed by the World Health Organisation (WHO). It comprises 10 items pertaining to lifetime (Part 1) and recent (Part 2) use of substances.

Psychological Recovery: Psychological recovery will be assessed using the Short Version (11 items + 1 personal goal) of the CHOICE (CHoice of Outcome In Cbt for psychosEs) scale (74). CHOICE was developed by our group in collaboration with experts-by-experience, reflecting themes they considered important psychological therapy outcomes.

Social and occupational functioning: This will be assessed using the Personal and Social Performance Scale (PSP (75)). It is a 100–point single-item rating scale based on the assessment of functioning in four areas (socially useful activities, personal and social relationships, self-care and disturbing and aggressive behaviour). For an impairment to be rated, it must relate to psychological problems rather than lack of opportunity.

Economic measures:

Health-related quality of life: Generic health-related quality of life will be measured using the 5-level version of the EuroQol 5-dimensions (EQ-5D-5L (76)), introduced by the EuroQol Group in 2009 as an alternative to the standard EQ-5D-3L, to provide greater sensitivity and to reduce ceiling effects. The EQ-5D descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). The score for each dimension can be combined into a 5-digit number that describes the person's health state.

Health-related quality of life for users of mental health services: We will additionally include the Recovering Quality of Life (ReQoL-10 items (77)), which may be more sensitive to

change than the EQ-5D, given the lack of evidence to support the use of the EQ-5D in more severe mental health populations (78).

Service-use: Service use will be measured in interview using a modified version of the Adult Service Use Schedule (AD-SUS), designed and successfully applied in psychosis populations (79). The AD-SUS measures use of all-cause health and social services appropriate for the NICE preferred NHS/Personal Social Services perspective (80).

Therapy group only:
Acceptability:

The participants will be offered interviews once they have finished therapy to explore acceptability and satisfaction with the therapy they received. Close attention will be paid to any emotional distress resulting from memory reprocessing procedures, in particular potential impact on psychotic symptoms, and whether this was considered unacceptable or unnecessary. The view of those who chose to end therapy early will be gathered at point of ending, using additional questions about their reasons for doing so and to identify barriers and potential solutions to engagement in therapy. Therapists will be interviewed once they have completed therapy with two or three participants to obtain feedback about acceptability, and any potential difficulties in delivery.

Experts by experience researchers with lived experience of psychosis will conduct the participant interviews, with appropriate supervision and support, and therapists will be interviewed by RWs. It is anticipated that the final patient sample will be representative and include variance on key variables (e.g., therapy engagement, age, gender, ethnicity, clinical presentation). All interview data will be recorded, with participants' permission, and transcribed verbatim for analysis.

Therapeutic alliance*:*
Therapeutic alliance between therapists and participants randomised to the intervention arm will be measured using the Working Alliance Inventory – Short Form Revised (WAI-SF-R (81). The therapist and client versions cover three key aspects of alliance: agreement on therapy tasks, agreement on therapy goals and the development of an affective bond (81). Both the self-report participant and therapist versions will be administered.

Plans to promote participant retention and complete follow-up {18b}

A number of strategies are planned to maximise participant retention into the trial and ensure completeness of outcomes, in addition to those mentioned in the risk and benefits section above.

A 1m window will be allowed for completion of assessments at each time point. Assessment measures will be clearly prioritised so that the most important will be collected first to avoid missing data. The CAPS-5 ((50); primary outcome) will always be administered first.

Participants who choose to end the therapy early or deviate from the allocation protocol (e.g., someone receiving trauma-focused therapy in the TAU group) will still be invited to complete all follow-up assessments. Participants will be remunerated for their time and travel, which secures good concordance with trial procedures, even in those who end

therapy early (82). Home visits will be arranged for participants who are unable to travel, or taxi fares paid if preferred. As a last resort, assessments can be done by remote means (such as video call or telephone). Anyone who moves within the UK will be followed up.

A mid-therapy assessment is included to minimise attrition from the trial (83), as 9m is a long period without contact with the research team for this population. This is particularly the case for the control group and those who end therapy early, and the extra assessment stage will provide data that can be used in the linear mixed model for the intention-to-treat analysis for those who drop out of the study at the primary endpoint. This adds some validation to a missing-at-random assumption for outcome missingness. The four 'keeping in touch' phone-calls will also help to retain participants in the trial until the final assessment 24m post randomisation.

Summary reports of the assessment findings will be written up and provided to participants and their clinical teams, with the participant's consent and time permitting; we have found this facilitates recruitment from teams and retention for participants into the trial, as well as ensuring liaison and involvement of teams.

Data management {19}

A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system. The EDC will be created in collaboration with the trial analyst/s and the Trial Coordinator and maintained by the KCTU for the duration of the project. It will be hosted on a dedicated server within KCL.

The PI or delegate (e.g., Trial Coordinator) will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the PI or delegate from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the PI or delegate in the first instance.

Participant initials and age will be entered on the EDC, but not NHS number, email addresses, participant names, addresses or full postcodes. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial. Source data will be entered by the RWs at each site, typically within 7 days of data collection by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trial of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Data quality will be ensured by close monitoring and routine auditing for accuracy throughout the data collection period. In order to ensure the accuracy of the data entered into the database, the main outcome measure entry will be checked for every participant by comparing the paper record with that on the database. An error rate of no more than 5% is acceptable. This will be done once all possible assessments for each time point have been completed. If the error rate is higher than 5%, advice will be sought from the trial statistician and methodologist regarding further data checking

The PI team will undertake appropriate reviews of the entered data, in consultation with the project analyst, for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

At the end of the trial, the site PI will review all the data for each participant to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

Upon request, KCTU will provide a copy of the final exported dataset to the PI in .csv format and the PI will distribute onward as appropriate.

Pseudonymised recordings of the qualitative interviews will be transcribed by a KCL approved transcription service. All recordings will be transferred and stored securely, and the transcription service will follow GDPR regulations (2018).

Confidentiality {27}

Clinical confidentiality

Issues relating to confidentiality will be addressed at the eligibility stage and potential participants will be advised of the limits of confidentiality (i.e. that the researcher will have a duty to inform health professionals if the participant discloses information which highlights any safeguarding or risk issues). It is also possible that disclosure of criminal or other acts potentially requiring action will occur during assessment and therapy sessions. The research team will be trained in both local and national policies for dealing with such disclosures and will follow our Standard Operational Procedures for managing risk disclosures. All RWs and trial therapists will have access to supervisory input to ensure appropriate action is taken with no delay. The limits of confidentiality and possibility of action arising from certain disclosures will be clearly noted in the information sheets. The potential participant will be offered at least 24 hours to consider all the information provided before written consent is obtained. Therapists will address confidentiality issues again with participants allocated to the TF-CBTp group at the start of therapy, and at any appropriate subsequent points during the therapy.

Data confidentiality

Research data will be confidential unless a participant discloses information that indicates that they or another person are at risk of harm. If harm is disclosed the RW or trial therapist would be required to share this information with the participant's care team (in line with NHS Trusts Safeguarding Vulnerable Adults policy) and documented in the NHS trust's electronic patient record system. The RW or trial therapist would endeavour to discuss this with the participant before confidentiality is broken. All participants will be informed of this during the written informed consent process and reminded of this at the start of the intervention, outcome assessments and qualitative interviews.

The only other exception where research data or Personally Identifiable Data (PID) may be accessed by another person outside of the research team is if individuals from the sponsor organisation (i.e. SLaM) and other regulatory organisations conduct a monitoring or audit visit. In this instance only the person/s conducting the audit may look at the participants' clinical and research records to check the accuracy of the research trial. All participants are made aware of this during the written informed consent process.

All data will be pseudonymised. Each participant will be assigned a unique screening number upon referral to the trial. This number will be written on all eligibility measures and databases. A unique trial identification number will then be issued following completion of the baseline assessment. This number will be written on all clinical assessment forms/datasheets and databases used to record data on participants. A hard copy of a record sheet linking PID (participant identity, contact details, trial identification number) for all participants will be kept separate from all the research data at each site. It will be placed securely in locked filling cabinets separate from research datasheets.

Due to the COVID-19 pandemic trial staff may have to work remotely, outside of Trust premises. An electronic version of the record sheet linking PID (participant identity, contact details, trial identification number) will therefore be created and saved on secure Trust drives accessible online.

Referral forms will contain PID. The PID obtained for the referral will be processed in line with Caldicott principles. The referral forms will be completed electronically in a Microsoft word document and saved password protected on a secure NHS Drive only accessible to the research team. The password will only be shared with the research team. Log of contact of the participant with research team, and of the research team with the clinical team, will be stored as above. All data will be kept secure at all times and maintained in accordance with General Data Protection Regulation (GDPR, 2018) requirements and archived according to clinical trial GCP regulations. Participant consent forms will be retained, kept confidential and stored securely. All identifiable data will be destroyed following a period of 10 years (as determined by relevant information governance policies) after the completion of the trial.

No participant identifiable information is recorded on the research assessment records and the computerised database is held centrally and managed by the KCTU. Data from the assessments are entered into this central record by RWs using a secure network connection.

Therapy files will be kept in a secure office and are not accessible to the staff collecting the research outcome data.

Recordings

Encrypted recording equipment (such as encrypted smart phone, laptop, or equivalent devices) will be used to record assessments (with participant consent) to check fidelity to assessment protocols and allow for multiple ratings of assessments to ensure interrater reliability. The therapy sessions will also be recorded (with participant consent) for monitoring the fidelity of the intervention delivery. These files named with a unique participant identifier will be transferred to secure central storage as soon as possible and stored as computer files on secure NHS/ University servers. Recordings of the therapy will be accessible to the participant's therapist, the supervisor, and a random selection to the independent fidelity rater.

The study will adhere to the joint guidance on secure recording issued by KCL and the NHS Trusts. When not in use, encrypted devices will be stored in a locked cabinet within a locked office. Each device will be password protected. In the event of the device being lost or stolen this will be reported as a data incident to the Information Management and Compliance Team at KCL and the Information Governance Team at the relevant NHS Trust. Any sensitive data on a lost/stolen device will be remotely erased.

Pseudonymised audio recordings of the qualitative interviews will be transcribed by a KCL approved transcription service. All recordings will be transferred and stored securely, and the transcription service will follow GDPR regulations (2018).

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/A

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

A detailed statistical analysis plan for the primary and secondary outcomes, including the economic analysis, will be approved by the DMEC and TSC before analysis of unblinded data.

Primary and secondary outcomes:

We will report data in line with the CONSORT-SPI (60) statement showing attrition rates and loss to follow-up (see Appendix 1). All analyses will be carried out using the intention to treat principle, incorporating data from all participants including those who do not complete therapy. Every effort will be made to follow up all participants in both arms for research assessments.

Analyses will be conducted in Stata version 15 or later. Descriptive statistics within each randomised group will be presented for baseline values. These will include counts and percentages for binary and categorical variables, and means and standard deviations, or medians with lower and upper quartiles, for continuous variables, along with minimum and maximum values and counts of missing values. There will be no tests of statistical significance or confidence intervals for differences between randomised groups on any baseline variable.

Treatment effects on primary and secondary outcomes will be estimated using linear mixed models. Fixed effects will be centre, baseline assessment for the outcome under investigation, group, time (categorical), and time*group interactions. Participant and therapist will be included as random intercepts. Marginal treatment effects will be estimated and reported for each time point as adjusted mean differences in scores between the groups with 95% confidence intervals and 2-sided p-values. For binary secondary outcomes, the same approach will be followed using logistic mixed models and effects will be reported as conditional odds-ratios.

The analysis will be conducted in two separate stages. The primary analysis will estimate treatment effects at the primary endpoint of 9m, using all outcome data from 4 and 9 months. Analysis will take place after the last participant has completed their 9m assessment, and will report the estimated effects at 4 and 9 months. The results will not be shared with the blinded assessors, nor outside of the STAR team, until all 24m assessments have been completed, to avoid any biases on data collection.

The secondary analysis will estimate treatment effects at 24m, using all outcomes from 4, 9 and 24 months. Analysis will take place after the last participant has completed their 24m assessment, and will report the estimated effect at 24m.

Cohen's D effect sizes will be calculated as the adjusted mean difference of the outcome divided by the sample standard deviation of the outcome at baseline. These will be displayed in a forest plot showing the therapy effects on the primary and the secondary outcomes at 9 months and 24 months post randomisation.

Missing data on individual measures will be pro-rated if more than 80-90% (depending on questionnaire) of the items are completed; otherwise the measure will be considered as missing. We will check for differential predictors of missing outcomes by comparing responders to non-responders on key baseline variables. Any significant predictors will be included in the analysis models. This accounts for missing outcome data under a missing at random assumption, conditional on the covariates included in the model. As a sensitivity analysis, we will assess whether therapy adherence is associated with missing data, and if it is associated, use inverse probability weights or multiple imputation to compare results.

Economic analysis

A within-trial cost-effectiveness analysis will be carried out, taking the NHS/personal social services perspective preferred by NICE (80). Service use will be measured in interview using the AD-SUS (79), at baseline (covering the previous 3-months), at the 4m, 9m and 24m follow-up points, and at the four 3-monthly phone calls (covering the period since previous interview/phone call, thus ensuring coverage of the full 24m period). Service use will be costed using nationally applicable unit costs (e.g., NHS Reference Costs for hospital contacts; Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care for community-based services; and the British National Formulary for medication). The TF-CBTp intervention will be directly costed taking a standard micro-costing approach (84). Data on therapist time will be collected from clinical records (number and duration of face-to-face contacts) and unit costs will be based on the mid-point of the therapists' salary, including all employer costs (National Insurance and superannuation) and appropriate overheads (capital, managerial, administrative etc.). The cost of supervision will be included and indirect time (for e.g., training, administration, meetings with other professionals) will be estimated using a questionnaire completed by each therapist on the time they spend on various direct and indirect patient-related activities.

The primary economic evaluation will be a cost-utility analysis carried out at the 9m endpoint (end of therapy) with outcomes expressed in terms of QALYs, calculated from the EQ-5D-5L (76), using the area under the curve approach (85). Given evidence to suggest the EQ-5D may not be particularly sensitive in psychosis populations, the new ReQoL measure (77) and the primary clinical outcome measure (CAPS-5 (50)) will be included in secondary economic analyses. All three economic evaluations will be repeated at the 24m follow-up to explore the longer-term impact of TF-CBTp compared to TAU.

Costs and QALYs will be compared at the 9m and 24m follow-up points and presented as mean values by trial arm with standard deviations. Mean differences in costs and 95% confidence intervals will be obtained by non-parametric bootstrap regressions to account

for the non-normal distribution commonly found in economic data (86). Cost-effectiveness will be assessed using the net benefit approach and following standard approaches (87). A joint distribution of incremental mean costs and effects for the two groups will be generated using bootstrapping to explore the probability that TF-CBTp is the optimal choice compared to TAU, subject to a range of possible maximum values (ceiling ratio) that a decision-maker might be willing to pay for unit improvements in outcomes. Cost-effectiveness acceptability curves will be presented by plotting these probabilities for a range of possible values of the ceiling ratio (88). These curves are a recommended decision-making approach to dealing with the uncertainty that exists around the estimates of expected costs and expected effects associated with the interventions under investigation and uncertainty regarding the maximum cost-effectiveness ratio that a decision-maker would consider acceptable. To provide more relevant treatment-effect estimates, all economic analyses will include adjustment for the variable(s) of interest and baseline covariates (89), which will be pre-specified and in line with the clinical analyses. The primary analysis will be a complete case analysis with the nature and impact of missing data, in particular those lost to follow-up, explored in sensitivity analysis.

Qualitative interviews

All interview data will be analysed using Thematic Analysis (90), which results in a rich and accessible account of qualitative data. This process involves systematically and iteratively coding information from interviews under main headings and subcategories, and using previous literature to support the validity of categories. Member checking strategies (91) will be employed for this stage of the analysis with participants, members of the research team and expert-by-experience consultants, to maximise the transparency and trustworthiness of the data. Data management and analysis will be supported by NVivo software. Analysis will occur in parallel with data-generation and will continue until thematic saturation is achieved (the point at which no new categories emerge). All trial documentation and data will be retained for a minimum of ten years, as stated in Clinical Trials Regulations.

Interim analyses {21b}

No interim analyses are planned.

Methods for additional analyses (e.g. subgroup analyses) {20b}

All additional analyses will be clearly specified in the Statistical Analysis Plan and reviewed by the TSC and DMEC.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The random effect structure of the main analysis will account for repeated measures and clustering due to the partial nested design. All models will be estimated using maximum likelihood estimation, which allows for missing outcome data under the Missing At Random assumption; we may also use inverse probability weighting to adjust for non-adherence to allocated treatment and other intermediate outcomes as predictors of future loss to follow-up. A dose-response model will be considered to estimate a linear effect of amount of therapy, with randomisation as an instrumental variable for the number of TF-CBT sessions attended.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The investigators will permit trial-related monitoring, audits and Research Ethics Committee (REC) review by providing the Sponsors, the DMEC and REC direct access to source data and other documents as required.

Anonymised datasets generated during and/or analysed during the current study will be available upon request post publication of the trial results from the Principal Investigator (EP), following review of appropriateness of request by the trial team.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The trial is hosted by SLaM NHS Foundation Trust. KCL is the trial sponsor (with SLaM as the co-sponsor). SLaM will be responsible for sub-contracting to all other participating Trusts and HEIs.

The trial has been carefully designed to ensure compliance with GCP and scientific integrity. The research programme development, design and implementation will be managed by the PI and the co-applicants, in consultation with experts-by-experience consultants and other expert collaborators from within and outside of the PI's institution. The trial will comply fully with KCTU Standard Operating Procedures. A dedicated Trial Coordinator post will assist in the day-to day management of the project reporting to the PI. A trial management group (TMG) will meet monthly; its membership will include the investigators, the Trial Coordinator and site leads. It will be chaired by the PI and will manage the day–to-day running of the study and ensure good communication between trial sites, receiving monthly reports from each site on recruitment, therapy completion, adverse events, reviewing progress against milestones and finding solutions to problems as they arise. It will oversee the preparation of reports to the TSC and DMEC. The PI and the co-applicants are highly experienced in working clinically with people with psychosis, and in carrying out research studies in this population.

The TSC will oversee the study on behalf of the of the trial Sponsor and Funder and ensure that the study is conducted within appropriate NHS and professional ethical guidelines. It will provide advice on all appropriate aspects of the project; will oversee progress of the trial, adherence to the protocol, participant safety and the consideration of new information of relevance to the research question; will ensure the rights, safety and well-being of the participants are given the most important considerations and should prevail over the interests of science and society; will ensure appropriate ethical and other approvals are obtained in line with the project plan; will agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments. It will comprise six independent members: a chairperson, a clinician, health economist, statistician, and two experts by experience.

Composition of the data monitoring committee, its role and reporting structure {21a}

The DMEC will monitor: (1) recruitment of study participants; (2) ethical issues of consent; (3) quality of data (including missing data and unblindings); (4) the incidence of Serious Adverse Events; (5) any other factors that might compromise the progress and satisfactory

completion of the trial. It will make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue, with the safety, rights and well-being of participants being paramount. It will consider the need for any interim analyses, including potential requests from the Funder, and will advise the TSC regarding the release of data and/or information. The DMEC will consist of three independent members: a chairperson, a clinical academic and a statistician.

Adverse event reporting and harms {22}

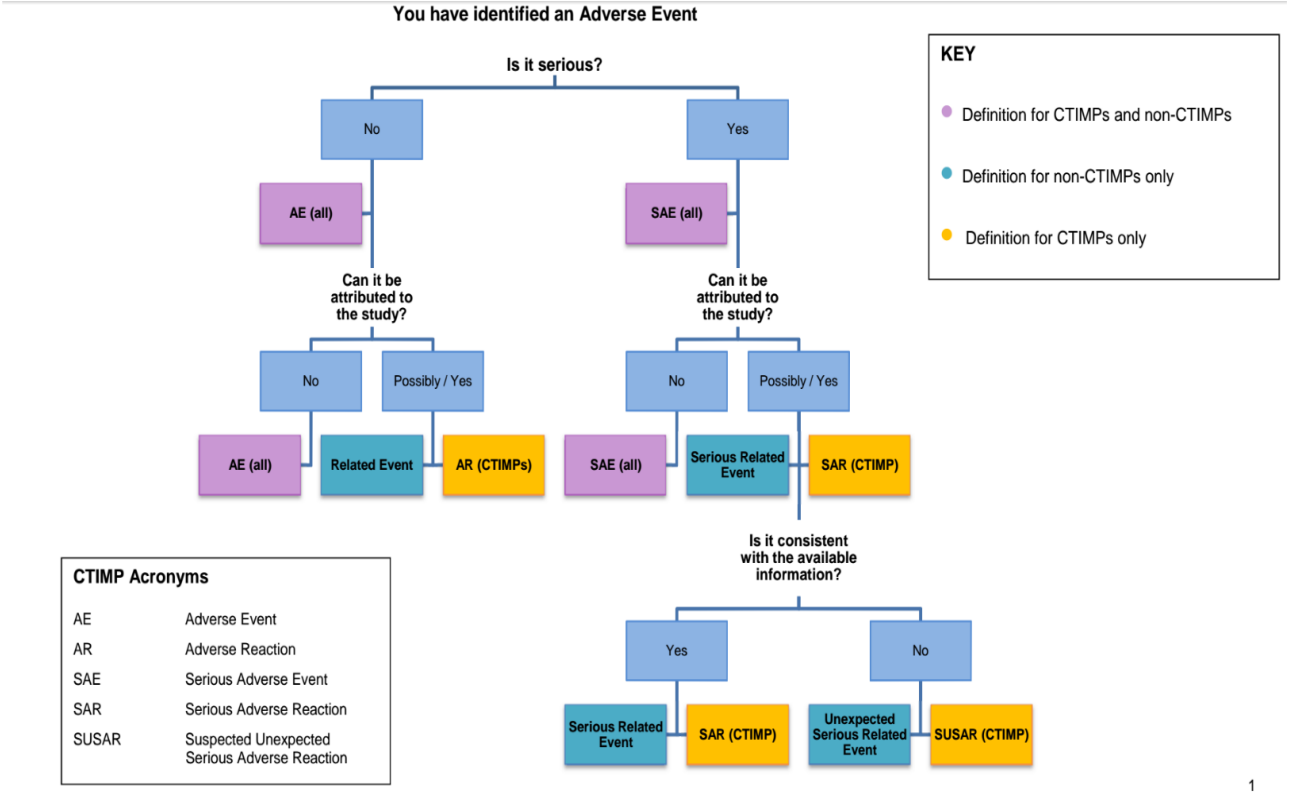
Best practice, professional guideline and local NHS policies for monitoring mental state and risk will be followed throughout the participants' involvement in the trial and will be facilitated by close liaison with clinical teams. The safety of the intervention will be monitored closely during therapy sessions and through regular contact with the participant's clinical team or GP.

The occurrence of adverse events (AEs) will be monitored actively and systematically and recorded by RWs and therapists, following guidance from the CONSORT-SPI (58) with the extension for non-pharmacologic treatment, and the extension for reporting of harms. Medical Research Council (MRC) GCP in Clinical Trials will also be followed to ensure good governance of the trial for integrity and participants' safety and wellbeing.

All AEs and participant withdrawals will be recorded and monitored by the trial team. If indicated, the Trial Coordinator/ Site Leads will review the clinical notes and contact clinicians for any important additional information. In order to ensure active surveillance of harms, at each assessment point, RWs will actively check for the occurrence of specific AEs using a structured checklist completed with the participant alongside the AD-SUS. At the completion of the trial, all clinical notes will additionally be checked, for the total duration of enrolment, for any previously undisclosed record of AEs. This extra procedure is to ensure completeness of records and to address the possibility of an increased likelihood of disclosure of AEs in the TF-CBTp condition, as a result of greater frequency of contact and the therapeutic relationship. For the final reports of the trial, the numbers, types and severity of AEs by trial condition, as well as discontinuations, will be reported, using descriptive statistics (since there are no pre-specified hypotheses concerning adverse events or harms, and, given the expected low frequency of AEs, the data will not be suitable for an ITT statistical analysis).

GCP guidance for non-CTIMPs studies (see Figure 2) will be followed to make decisions regarding seriousness (i.e., AEs vs SAEs), relatedness to the trial (i.e., Related Events (REs) and Serious Related Events (SREs), and Unexpected Serious Related Events (USREs).

Figure 2: GCP Decision Tree for Adverse Events



AEs are defined by the Health Research Authority (HRA) as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in participants, whether or not related to the treatment. In addition, issues specific to psychological therapies (92, 93), and for specific concerns clinicians have about trauma-focused therapy in psychosis individuals, will also be monitored, namely: clinically significant increases in mental health problems and/or risky or problematic behaviours; harm to self/others, including suicide attempts; harm from others; emergency room visits or crises. Clinically significant increases will be operationalised as an unresolved exacerbation requiring increased involvement from the care team, eg requiring a change in treatment plan. Distress or complaints associated with therapy, completion of assessment measures, or any other trial procedure would also constitute AEs.

The causes for the AEs will also be recorded and monitored. For each AE, the following potential reasons will be identified: victimisation (aggressive behaviour, sexual abuse/assault, physical abuse/assault, emotional abuse/psychological maltreatment, exploitation, and other victimisation); mental health/psychological problems (excessive use of substances, general distress, psychotic symptoms, PTSD symptoms, suicidal ideation, and other psychological); trial procedures (group allocation, assessments, or therapy); physical health, including COVID-19; accidents or natural disasters; and other.

AEs will be initially assessed at three levels of severity; mild, moderate and severe, which reflect the impact of the event on the person at the time. Please note there is a distinction between “severe” and “serious”. Seriousness is the criteria for defining regulatory reporting obligations: SAEs are defined as death and life-threatening events (Category A), incidents which acutely jeopardise the health or psychological wellbeing of the individual, resulting in immediate hospital admission and/or persistent or significant disability or incapacity

(category B), or resulting in injury requiring immediate medical attention (category C). However, in this study any AE rated as 'severe' will automatically be classified as an SAE.

All AEs and SAEs (from each site) will be pooled and reported monthly to the TMG and at each meeting of the DMEC, or at any time at the request of the DMEC Chair; there are no AEs or SAEs that do not require reporting in this trial, as it is an important subsidiary goal of the trial to establish the safety of the intervention. Urgent actions concerning participant and staff safety, communication with others, and clinical care will be immediately addressed by the Trial PI and Site Leads and reported to the TMG.

AEs will be categorized for severity and seriousness by the site leads/Trial Coordinator. SAEs will be further reviewed for relatedness to trial procedures and unexpectedness by the PI initially, and additionally by the chair of the DMEC.

Relatedness and unexpectedness of an event to the intervention will be judged based on the following:

1. Related: the event resulted from administration of any of the research procedures, judged according to a temporal relationship (i.e., SREs);
2. Unexpected: the event is unexpected or unexplained given the participant's clinical course, previous conditions and history, and concomitant treatments (i.e., USREs)

Only SAEs that have been judged by the PI and the chair of the DMEC to be USREs will be reported to the main REC. The DMEC will be responsible for investigating further, if there are any concerns about unexpectedly high rates of SAEs, SREs or USREs, which may include being unblinded as to trial condition or seeking further data on adverse events, and will advise the TSC on any ethical or safety reasons why the trial should be prematurely ended. The Funder will immediately be notified on receipt of any information that raises material concerns about safety or efficacy, and of any recommendations from the DMEC to end the trial. A flowchart displaying the recording and reporting of AEs and SAEs is provided in Appendix 5.

Frequency and plans for auditing trial conduct {23}

It is anticipated that the DMEC and TSC will be convened on a six-monthly basis, but either the research team or the DMEC/TSC will have the opportunity to request an increased frequency of meetings, should it be indicated.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any subsequent amendments to the protocol will be submitted to the TSC/DMEC, the Funder, and the REC and Regulatory Authorities for approval. They will be communicated to trial registries, journals and trial participants, as appropriate. The PI will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor.

Dissemination plans {31a}

We anticipate the key beneficiaries of our research to be people with psychosis who have experienced trauma; academics; clinicians and mental health service providers; NICE

guideline development group. It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals, and will be made available to participants and clinical teams in an accessible format and on the study website. It will also be accessible in print and digital media and presented at stakeholder's events. One of the key outputs of this study will be the publication of the final, detailed therapy manual, which will include specific guidelines for the delivery of therapy and operational guidelines for its application, including case examples. 'Case examples' materials will also include the opportunity for participants who received the therapy to contribute in a range of formats e.g., sharing testimonies and recovery stories on the STAR website, in journal articles or books, infographics etc. Lived experience accounts could be in audio, video or written blogs, or co-produced with their therapist, at the choice of the person. A key aspect of the long-term dissemination will be through settings associated with health-care provision, such as presentations and workshops for CBT practitioners and health-care managers.

Discussion

Improving access to psychological therapies and the implementation of trauma-informed care are key issues for NHS services. The proposed therapy, if acceptable, will provide a new, integrated psychological therapy for people with complex mental health problems whose needs are often not met by mental health services. The outcomes of this study, if positive, will be immediately useful to patients, clinicians, and clinical services. The proposed intervention has the potential to provide significant benefits to the significant number of people who have experienced trauma in terms of reductions in distressing post-traumatic stress, psychosis, and other symptoms. If found to be acceptable, the therapy could overcome obstacles in therapy delivery in clinical practice due to clinicians' concerns about the potential of trauma-focused therapy to exacerbate psychosis symptoms. Lastly, it has the potential to be cost-effective to service providers through reduced service use.

The availability of a detailed therapy manual will enable the therapy to be applied by CBT-trained therapists throughout the NHS. There are current plans for a significant expansion of training in CBTp nationally by NHS-England (NHS-E), which will be timely for maximum impact of the manual, as it can be embedded within the curriculum of the national training programs.

The main barrier to providing immediate patient benefit is likely to be a lack of resources for the implementation of the therapy. However, providing parity of care for mental health is an ongoing, pan-party government agenda. The development of psychological interventions for psychosis, specifically, is a current NHS priority, with recent investments by NHS-E in Improving Access to Psychological Therapies – Severe Mental Illness (IAPT-SMI) demonstration sites (94), and the implementation of national standards for the access and waiting times for psychological therapies in EIP (95) services. The remit of IAPT-SMI has since expanded (now renamed PT-SMI (Psychological Therapies for SMI)), with training plans contributing to a national agenda for increasing the workforce. The recent inclusion in NICE guidelines of the necessity to assess and treat trauma symptoms in people with psychosis in EIP services, is an indication that this topic is timely and will remain highly relevant to the needs of the NHS. Pathways to specialist trauma therapy are also integral to the provision of trauma-informed care, which is recommended in the NHS Long Term Plan as the model for community services in adults with severe mental health

problems (51). A failure to treat trauma sequelae in psychosis is itself costly to patients, their families, and the NHS. Should the therapy prove cost-effective, it will provide evidence to Clinical Commissioning Groups (CCGs) that investing in this treatment will save money in the long run.

Trial status

This protocol is Version 3.05 (DATE: 22.03.2024). Recruitment is planned to start in October 2020 and to last 31 months until April 2023.

Declarations

Acknowledgements

We would like to thank the experts-by-experience in the Manchester SURG and the PICuP Clinic Peer Supporters, who have provided advice in terms of highlighting the need for the research, the design of the trial, the measures selected and procedures for the conduct of the screening and assessments. We acknowledge the CRN for support in identification and recruitment of participants. RE is part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, and NIHR Research Professorship, NIHR300051).

Authors' contributions {31b}

EP is the PI of the study and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EP took responsibility for the main drafting of the protocol and made substantial contributions to conception and design. AH, RD, FV, KG, CS, AM took responsibility for the drafting of the protocol and made substantial contributions to conception and design. NK, AH, SB, NG, RD, CS took responsibility and made substantial contributions to the design and development of the clinical intervention and therapy fidelity. RE is accountable for the statistical plan and analyses and made substantial contributions to conception and design. SB and MH took responsibility and are accountable for the design and analysis of the economic evaluation. EL took responsibility and is accountable for the qualitive interviews design and analyses. RU, SS are the Trial Coordinators and contributed to the development of the trial protocol. DF, DT, EK are collaborators on the study and made substantial contributions to conception and design. All authors have been involved in drafting the protocol or revising it critically for important intellectual content. All authors read and approved the final protocol.

Funding {4}

This trial is funded by NIHR (HTA), NIHR128623. The Funder reviewed and approved the content of the protocol, but does not have a role in data collection, management, analysis, or interpretation; nor in the writing of the final report or decision to submit the report. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Availability of data and materials {29}

The Investigator(s) will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), the DMEC and REC direct access to source data and other documents as required.

An anonymised version of the main outcome data will be available from the trial team on reasonable request after publication of the main results paper.

Ethics approval and consent to participate {24}

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005. This protocol and related documents will be submitted for review to one of the registered England RECs, depending on availability.

Consent for publication {32}

N/A

Competing interests {28}

EP, AH, RD, FV, KG, CS, SB, NK, EL, DF, DT, RU, SS, NG, AM provide psychological therapies for individuals with psychosis and/or PTSD in NHS settings, and EP is the Director of a psychological therapies specialist service for psychosis (PICuP). CS, DF, DT, EK, AM, NK have written manuals for psychological therapies for psychosis for which they receive book royalties (from APPI; Guildford; Wiley; Routledge; New Harbinger). EP, AH, RD, FV, KG, CS, SB, NK, EL, DF, DT, NG, AM receive fees (or generate fees for their clinics or research units) for workshops and presentations on psychological therapies for psychosis and/or PTSD; EP, AH, RD, FV, KG, CS, RE, EL, DF, DT, AM hold or have held grants to carry out trials of psychological therapy for individuals with psychosis. Richard Emsley is a member of the HTA Clinical Evaluation and Trials Board.

Author details

See above.

Authors' information (optional)

N/A

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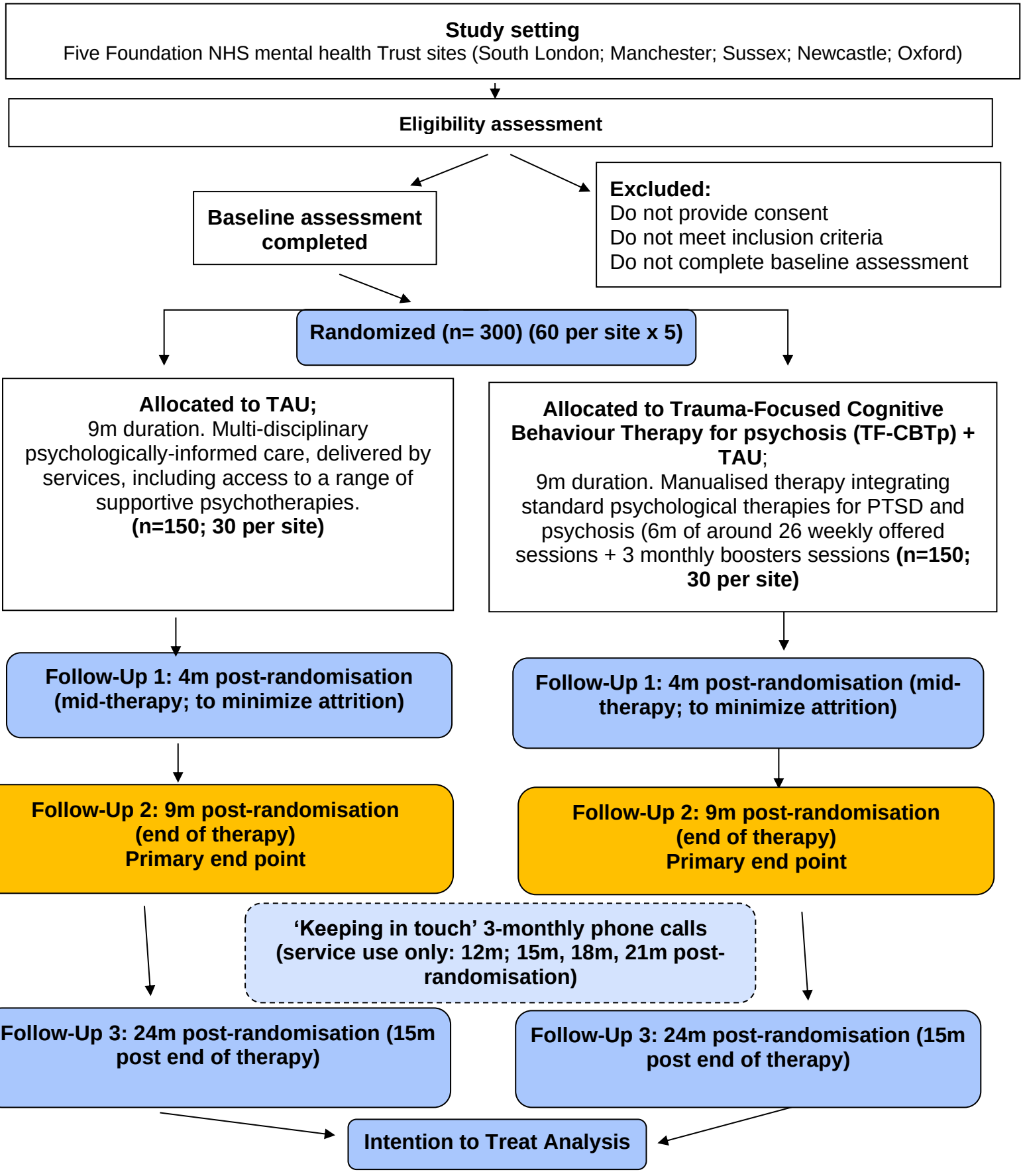
Appendix 1

Figure 3: CONSORT Diagram: **S**tudy of **T**rauma **A**nd **R**ecovery **(STAR)** trial



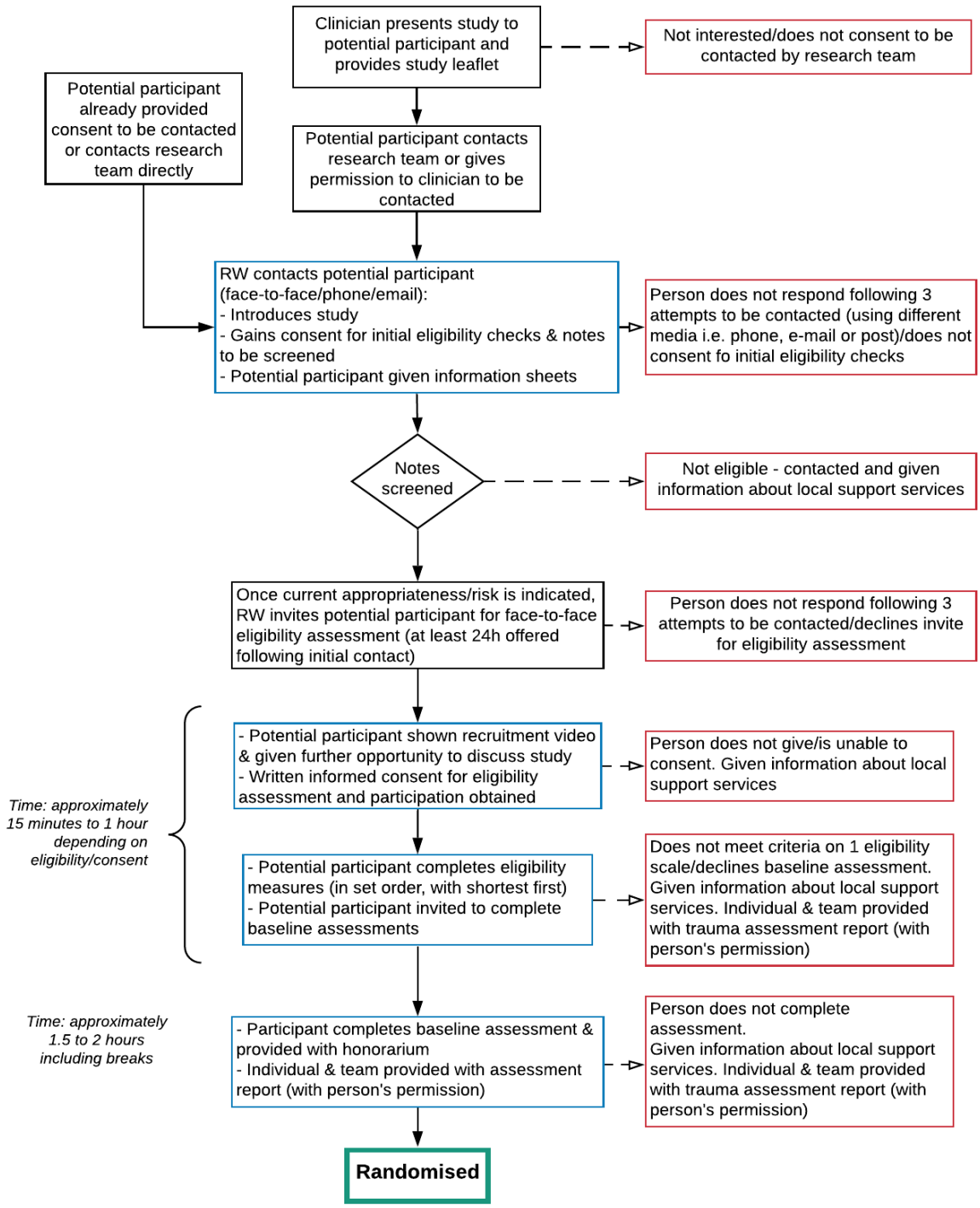
Appendix 2

Table 1: Internal pilot progression criteria

Criteria	How assessed	Time of check (from start of recruitment)	Go	Refine	Stop
Recruitment	% of target recruitment	6m (when around 20% of total recruitment should have been completed ie N=60) 12m (when around 50% of total recruitment should have been completed ie N=150)	≥80% of anticipated recruitment rates (minimum of 48 participants recruited) ≥80% of anticipated recruitment rates since last check (minimum 72 participants recruited between 6m and 12m post recruitment start)	50-79% of recruitment rate (between 30–47 recruited)	Recruitment rates <50% (≤29 recruited) Recruitment rates <80% between 6m and 12m post recruitment start (≤71 recruited), despite amendments implemented
Therapy attrition	% who drop-out of therapy (attending <6 planned sessions during 9m therapy envelope, at least 1 of which should be in Phase 3)	12m (when 7% should have completed therapy) 16m (when 25% should have completed therapy)	≥75% therapy completion rates ≥75% therapy completion rates since the last check (i.e., between 12m and 16m post recruitment start)	50-74% therapy completion rates	Completion rates <50% Completion rates <75% between 12m and 16m post recruitment start, despite amendments implemented
Assessment attrition	% who provide data on primary outcome at end of therapy (9m) or 4m (mid-therapy) assessment	12m (when 7% should have completed mid- or end of therapy assessment) 16m (when 25% should have completed mid- or end of therapy assessment)	≥80% assessment completion rates ≥80% assessment completion rates since the last check (i.e., between 12m and 16m post recruitment start)	50-79% assessment completion rates	Primary outcome data provided by <50% Primary outcome data provided by <80% between 12m and 16m post recruitment start, despite amendments implemented
Therapy adherence	Independent adherence ratings from therapy tapes	Throughout therapy delivery	≥80% rated as acceptable quality	50-79% rated as acceptable quality	Acceptable quality rated for <50% of therapy tapes

Appendix 3

Figure 4: Identification and consent plan



Appendix 4

Figure 5. Schedule of enrolment, interventions, and assessments.

	TRIAL PERIOD									
	Enrolment	**Allocation**	**Post-allocation**							**Close-out**
TIMEPOINT	***-t_1***	**0 *(baseline; pre-therapy)***	***t_1 (2 weeks; start of therapy***	***t_2 (4m; mid-therapy)***	***t_3 (9m; end of therapy)* PRIMARY ENDPOINT**	***T_4 (12m)***	***t_5 (15m)***	***t_6 (18m)***	***t_7 (21m)***	***T_8 (24m; final assessment)***
ENROLMENT:										
Approach from clinical teams	X									
Consent for initial eligibility check and risk screen	X									
Consent for eligibility assessment and participation	X									
Allocation		X								
INTERVENTIONS:										
TF-CBTp + TAU			←	—	→					
TAU			←	—	→					
ASSESSMENTS:										

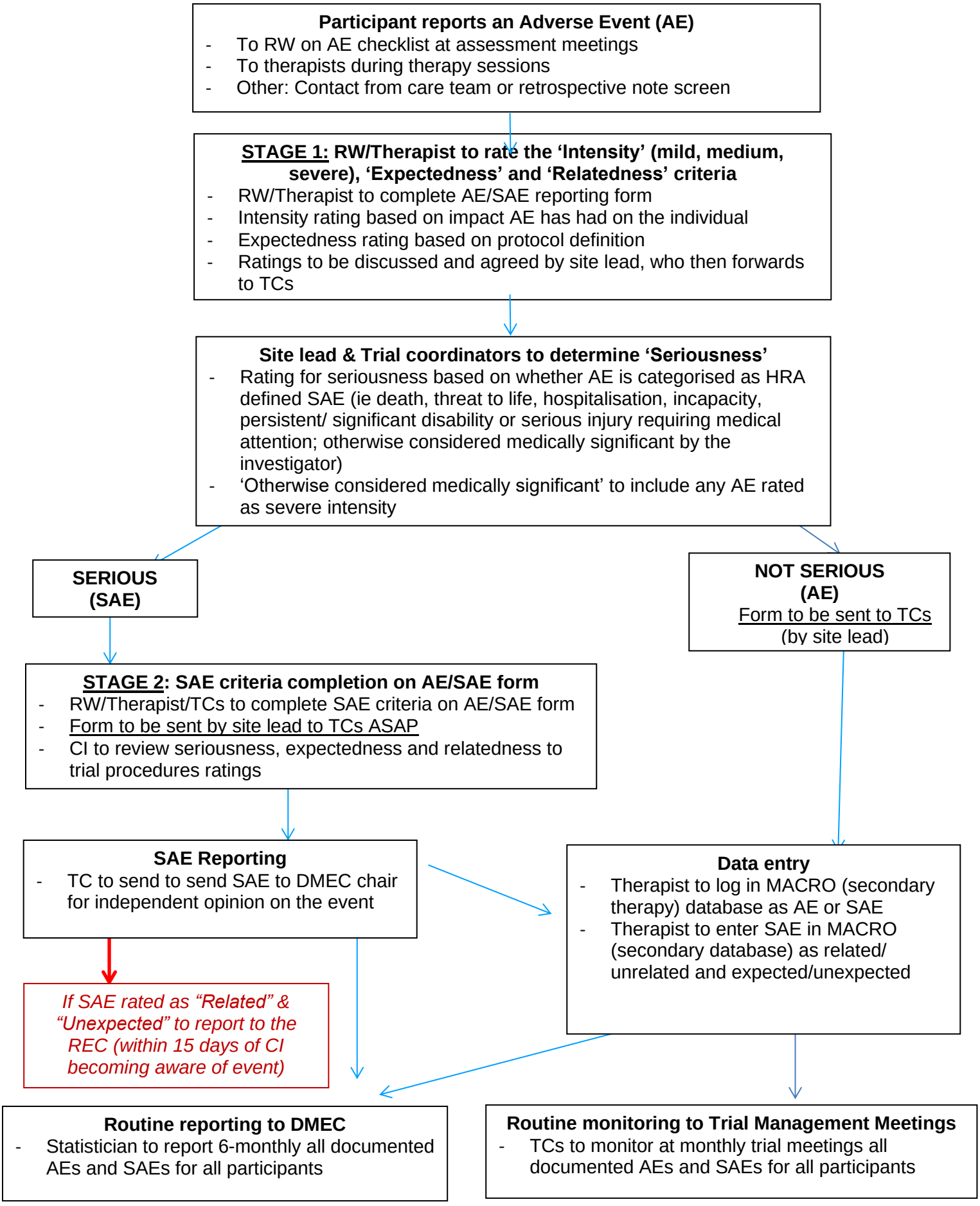
Eligibility measures (in order of administration): ***SSD diagnosis (case-note review)*** ***PSYRATS (distress intensity item)*** ***Mini-TALE*** ***PCL-5 (re-experiencing items)*** ***CDSS (suicidal risk probes)*** ***Full TALE*** ***CAPS-5***	X *(participants who do not meet criteria on 1 scale will not be administered the next)*									
Symptom measures: ***Demographics form*** ***CAPS-5*** ***ITQ*** ***PTCI-9*** ***DSPS*** ***PSYRATS*** ***GPTS-R*** ***DASS-21*** ***PSFS*** ***ASSIST*** ***CHOICE*** ***PSP***		X *(participants will have already completed CAPS-5 as part of eligibility assessment)*		X	X					X
Economic measures: ***EQ-5D*** ***ReQoL-10***		X		X	X					X
AD-SUS		X		X	X	X	X	X	X	X
Therapy group and therapists: Qualitative interviews					X					

WAI			X (therapy session 3	X (therapy session 13)						
Non-outcome assessments: Adverse Events (AEs) checklist				X	X	X	X	X	X	X
COVID-19 Context questionnaire		X		X	X	X	X	X	X	X
Feedback form		X								X

Calgary Depression Scale (CDSS; (94); 4 probes for suicidal ideation)
Mini-Trauma And Life Events (TALE) checklist (4 items + 1 open ended question (43))
PTSD Checklist for DSM-5 (PCL-5; (34); 5 re-experiencing items only)
Full length TALE checklist (44)
Clinician Administered PTSD Scale (CAPS)-5 (50))
Psychosis Symptoms Rating Scales (PSYRATS (48)) Hallucinations in non-auditory modalities (i.e., visual, somatic, olfactory, sense of presence), and multimodal experience, will also be assessed
International Trauma Questionnaire (ITQ) (63)
Brief Version of the Posttraumatic Cognitions Inventory (PTCI-9 (64))
Dissociative Subtype of PTSD Scale (DSPS; 15 items; (65),
Revised version of the Green et al Paranoid Thoughts Scale (GPTS-R) (69)
Short form of the Depression Anxiety Stress Scales (DASS-21 (70))
Paykel Suicidal Feelings Scale (PSFS; (71))
Brief Version of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST; (72)
Short form of the CHOICE (CHoice of Outcome In Cbt for psychosEs) scale (74)
Personal and Social Performance Scale (PSP (75))
5-level version of the EuroQol 5-dimensions (EQ-5D-5L (76))
Recovering Quality of Life for users of mental health services measure (ReQoL-10 (77))
Adult Service Use Schedule (AD-SUS (79))
Working Alliance Inventory - Short Form Revised (WAI– F-R (81))

Appendix 5

Adverse Events and Serious Adverse Events Flowchart



Appendix 6
SOP 10 COVID Remote Trial Delivery

Study of Trauma And Recovery

SOP 10
COVID REMOTE TRIAL DELIVERY
V1 22/07/2020

Revision History			
Version No.	**Effective Date**	**Author**	**Description**
1	22/07/2020	Sarah Swan Raphael Underwood (Trial coordinators)	Adaptation to procedures to ensure safe and ethical delivery of trial activities within the context of the COVID-19 pandemic.

Approved by (Name, title, signature): *Date:*

_____ _____

Contents

1. Purpose

The standard operating procedure (SOP) has been created to provide guidance on how to safely continue with STAR research activities within the context of the COVID-19 pandemic and physical distancing restrictions.

2. Scope and Responsibilities

The SOP applies to the entire STAR research team (chief investigator, principle investigators, co-applicants, trial coordinators, trial therapists and research workers) engaged in activities related to the STAR trial. This SOP shall be applicable for the entirety of the global COVID-19 pandemic. The SOP will be followed in line with national government guidance, local Trust policy and procedures and the NIHR restart framework regarding COVID-19.

3. Objectives

To ensure clear adaptations to "standard practice" are outlined and adhered to across sites, for:

I. All relevant individuals regarding attendance at trial meetings
II. All research workers regarding clinical team liaison (stage 1 recruitment)
III. All research workers regarding participant recruitment (stage 2 recruitment)
IV. All research workers regarding participants assessments
V. All therapists regarding STAR therapy delivery
VI. All relevant individuals regarding ongoing supervision and training

4. Background

COVID-19 is a new strain of the virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). This group of viruses is common, and found across the world. The majority of those whom contract the virus will experience mild to moderate respiratory illness, recovering without the need for any medical intervention. Common symptoms include fever, shortness of breath, cough and anosmia (loss or change of smell/taste). For some groups, there is a greater risk of the virus developing into a very serious illness which can lead to death. Clinically vulnerable groups include: those over the age of 70; those with an underlying chronic health condition (such as asthma, COPD, heart disease, diabetes); those with a weakened immune system and pregnant women. Those from Black, Asian and minority ethnic groups are also at greater risk of both contracting COVID-19 and having a worse outcome than their White counterparts.
In response to the COVID-19 pandemic, the UK government initiated a national "lockdown" in March 2020 and set out guidance outlining measures to reduce the spread of the virus and to protect vulnerable groups. A phased approach to the nation's recovery is currently underway, with restrictions and guidance changing regularly to control the virus whilst also having the lowest health, economic and social cost.

5. Implications

COVID-19 has had a significant impact on the trial, as a result of the national and local restrictions to control the spread of the virus. Both the STAR team members and trial participants alike will have varying degrees of vulnerability to COVID-19 which must be taken into account in the delivery of the trial. Many of the individuals suitable to take part in the STAR trial will be classed as higher risk due to the factors outlined above, the high

occurrence of physical heath co-morbidities in a psychosis population and the effects of psychotropic medication.

It is highly likely that for at least some proportion of the STAR trial, we will be operating with a backdrop of physical distancing restrictions. STAR activities will need to be adapted in response to these to ensure ongoing adherence to good ethical study delivery that is also safe and concordant with COVID-19 government guidelines, local Trust policy and the NIHR restart framework.

The issues above are likely to have implications for:

- Trial meetings (such as the monthly trial management meeting, quarterly face to face meeting, Trial Steering Committee meeting, Data Monitoring meeting and any local site meetings)
- Liaison with local clinical teams and the role clinical staff play in the first stage of recruiting participants
    - Delivering face to face presentations for trial promotion
    - Clinical team staff identifying potential participants (referrals to the trial)
    - Clinical team staff making initial contact with potential participants to gain verbal consent for the STAR researchers to contact them
- Meetings with potential participants to recruit them into the study
- Completing the research assessment batteries at baseline and follow up
- Therapy delivery
- Supervision and Training
    - Availability and ability to attend local Trust related training
    - Delivery of and ability to attend in-house STAR training
    - Regular supervision for trial therapists and research workers

6. Procedures

Note - There is an expectation that any adaptations implemented will be the <u>least</u> restrictive option available however procedures must still adhere *fully* to national and local Trust policies *at all times.*

6.1 Trial Meetings (TMM, Quarterly, TSC, DMEC, Local Meetings)

All staff should complete their local Trust <u>COVID-19 Risk Assessment</u> to document their COVID-19 risk status. If for any reason this is not possible, the individual should complete the <u>STAR COVID-19 Staff Risk Assessment as an alternative.</u> In either instance, a copy should be sent to the PI, CI & trial coordinators. For external committee members (such as those in the TSC & DMEC), the trial coordinators will contact them prior, to complete the <u>COVID-19 Staff Risk Assessment</u>. Copies of these forms shall be stored confidentially (electronically) on Trust drives.

Risk assessments, national and local guidelines should be taken into account to determine the most appropriate means of conducting team meetings. Meetings should be adapted in the following ways:

- Conduct meetings remotely wherever possible, using a video conferencing platform (such as Microsoft Teams or alternative secure platform in line with local policy)
- For any face to face meetings, all attendees must maintain physical distancing and employ the use of PPE (face mask).
    - All staff should be offered the option to attend remotely, with priority given to those assessed as moderate/high risk.
    - Any staff member assessed as significant risk will be supported to attend meetings remotely at all times.

6.2 Team liaison (Stage 1 recruitment)

Presenting to clinical teams

In the event of physical distancing restrictions, the STAR research worker should first liaise directly, via telephone or email, with the team leader/manager and/or lead psychiatrist of any team the research worker is already scheduled to or planning to visit. Depending on the severity of the physical distancing restrictions, the research worker should propose an appropriate course of action from the following options:

- Attending the clinical team base, maintaining physical distancing and the use of PPE, to present the trial in person to the clinical team according to SOP 8 Recruitment (Team and Participant)
- Attending a virtual team meeting (conducted via Microsoft Teams or alternative secure video conferencing platform in line with local policy) to present the trial remotely to the clinical team. Following this the research worker should send an email to all the clinical team members including handouts of the presentation, staff contact cards & related promotional materials.

If meeting the wider team is prohibited:

- Attending the clinical team base, maintaining physical distancing and the use of PPE, to present the trial in person to the team leader and/or psychiatrist. The research worker should provide handouts of the presentation, staff contact cards & related promotional material for dissemination to the wider team when possible. An email to all team members with trial information and promotional material should be circulated.
- Attending a virtual meeting with the team leader and/or psychiatrist (conducted via Microsoft Teams or alternative secure video conferencing platform) to present the trial remotely. An email to all staff with trial information and promotional material should then be circulated.
- Telephone meeting with the team leader and/or psychiatrist to discuss the trial. An email to all clinical team members with trial information and promotional material should be circulated.
- Email contact with the team leader and/or psychiatrist, to gain consent for research worker to disseminate trial information and promotional material to their clinical team members via email.

Note - Every effort should be made to explore the possibility of a joint recruitment strategy with other trials recruiting from the same population/teams, in order to reduce burden on teams.

Identification of potential participants (referrals)
Where COVID-19 prevents clinical teams from identifying new potential participants, the STAR research worker should:

- Explore alternative sources of potential participants such as local research register databases where individuals have given their consent to be contacted directly about research studies
- Review the participant recruitment spreadsheet for existing referrals:
    a. who have not yet been followed up
    b. who have been placed on hold
- Maintain close communication with the clinical team leaders and psychiatrists to regularly review the situation in line with changes to local and national guidance

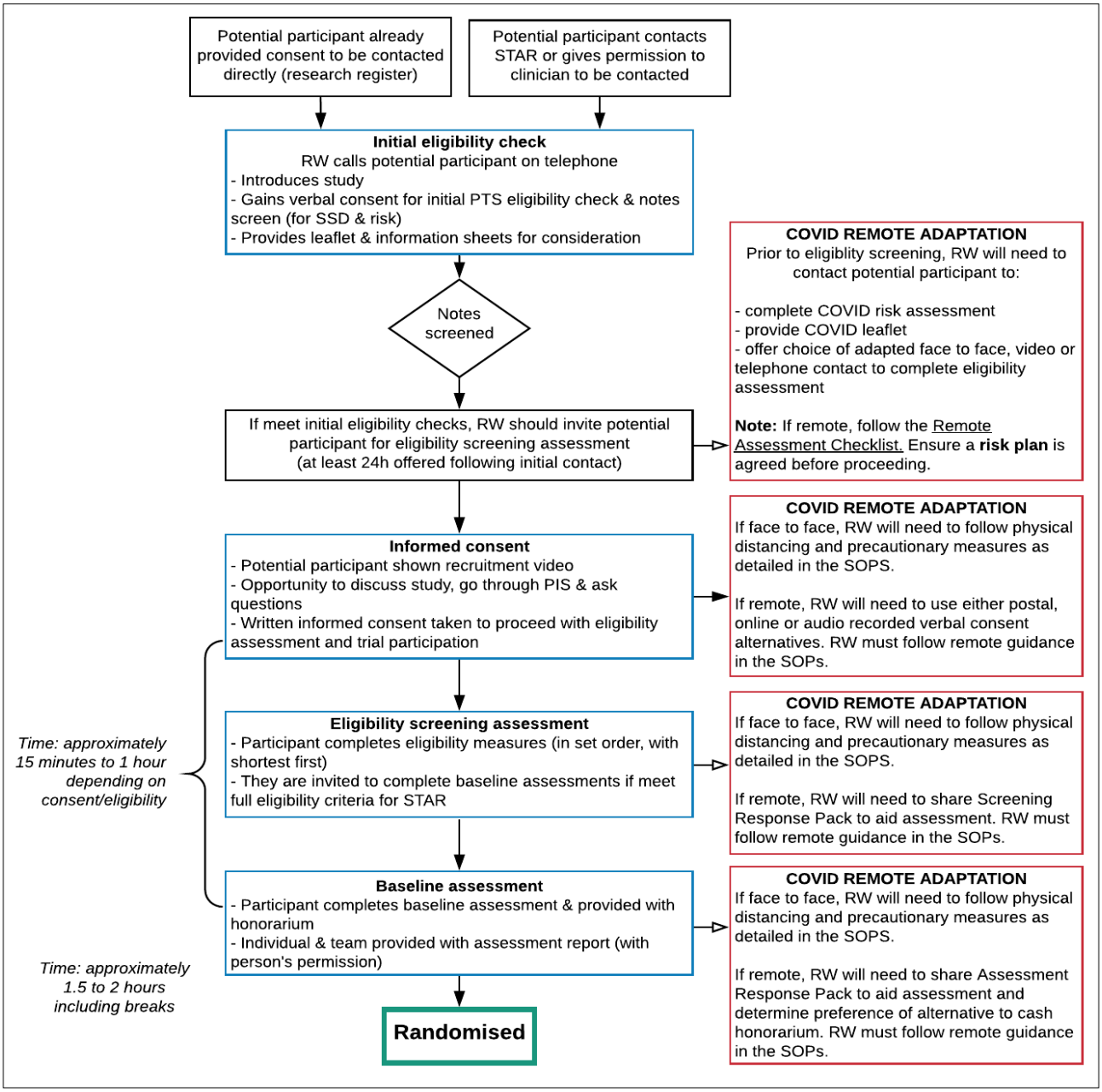
***Staff telling their patients about STAR and gaining initial consent to be contact*ed**
Where COVID-19 poses challenges to staff discussing the trial with their patients and gaining initial consent to be contacted by STAR researchers, the STAR research worker should:

- Liaise with individual members of staff to agree a plan around different options of informing their patients about STAR (text, email, telephone, face to face). Plans should remain under regular review.
- Ensure all staff have copies of promotional material which may be helpful.
- Keep up to date records of any agreed plans in the participant recruitment spreadsheet (COVID-19 tab)

6.3 Participant recruitment (Stage 2 recruitment)

Where clinical teams are able to continue to provide referrals to the STAR trial, the research worker should proceed with standard practice of contacting the individual over the phone to complete initial brief eligibility checks (see Identification and Consent diagram below). Any individual who meets the initial eligibility criteria will be invited for a follow up meeting to complete a consent form and further screening measures. The research worker should send the COVID 19 Leaflet (via the post or email) and complete the COVID 19 Participant Risk Assessment with the participant ahead of this meeting.
The current national guidelines regarding physical distancing, the risk assessment and local Trust policy should be used to inform which type of contact is most appropriate for this meeting. The individual should be offered a choice, where possible, from the options below:

- A face to face (adapted) meeting
- A virtual meeting (conducted via Microsoft Teams or alternative video conferencing platform)
- A telephone meeting



Note - the research worker must show sensitivity to the individual's level of comfort and familiarity with technology. This may mean that even if a video call was preferable, a telephone call may be best suited to that individual's personal circumstances.

The procedure for each is outlined below in more detail:

Face to face (adapted)

- The research worker should contact the individual (text/phone) on the day of the meeting to confirm the individual is not experiencing any symptoms of illness
    - If they are, the meeting should be rescheduled for 2 weeks later, or changed to take place remotely

- The research worker should explore which venue would be most appropriate to conduct the meeting (Trust premises, individual's home, an outside space such as a garden or public area)
- The research worker should employ physical distancing
- The research worker should avoid any physical contact with the individual
- The research worker (and wherever possible the individual) should employ the use of PPE (such as face masks/coverings, visors, gloves)
- The laminated Screening Response Pack should be cleaned prior to and following all meetings with disinfectant wipes
- The research worker should wash their hands/use alcohol gel prior to and following all meetings
- Surfaces within the room shall be cleaned prior to and following each meeting

Virtual (video) & telephone meetings

At the start of a remote meeting, the research worker should verify the individual's identity (especially for an initial meeting) to ensure they talking with the intended person. The research worker should follow the Remote Assessment Checklist to discuss and problem solve setting up the remote meetings to ensure they run as smoothly as possible. The discussion should include:

1. Checking out the practicalities, ensuring the participant has:
    - Sufficient mobile data/internet access/ or Wi-FI
        - If the individual does not have sufficient access the research worker should problem solve around alternative locations to access wifi, discuss whether the access to wifi and/or data is likely to change in the next coming days (for example individual may plan to buy credit shortly) or agree to use an alternative method such as telephone as opposed to video.
    - Ensuring the individual has knowledge of how to use any platforms/technology you may be using for the assessment
        - If the individual does not have sufficient knowledge/skill, the research worker should sign post the individual to an accessible "how to" resource for that platform, support the individual in a walk-through of the technology, offer a practice run or agree to use an alternative method such as telephone as opposed to video.
    - Checking explicitly on the level of confidentiality of the individual's environment.
        - The assessment may need to be rescheduled if the participant is unable to speak openly.
    - Checking more generally that the environment is quiet and ideally be low risk of interruption
2. Agreeing a contingency plan if the connection is lost or technical issues arise
    - If video connection is lost, the agreement may be for the research worker to make 2 immediate attempts to re-establish the video call. If this were to fail,

the research worker would send a text message to inform the individual they were going to attempt another video call on an alternative platform. If this were to fail, the research worker would send a text message to inform the individual they were going to initiate a telephone call instead to facilitate the rest of the assessment.

- If telephone connection is lost, the agreement may be for the research worker to make 2 immediate attempts to re-establish the call. If this were to fail, the research worker would send a text message to inform the individual they were going to attempt another call on an alternative number the individual would have provided in advance. If this were to fail, the research worker would send a text message to reschedule the remainder of the assessment.

3. Agreeing a remote plan for managing distress and risk (see SOP 4 Risk and Disclosure for further guidance). Broadly however this would include:
    - Collaboratively discussing and agreeing a plan for what the participant and research worker will do if the participant becomes distressed during the meeting. This must include that the research worker will contact the participant's clinical team if the participant becomes distressed and terminates the call and the research worker cannot re-establish contact.
    - Briefly documenting the plan (brief bullet point summary) on the participant's COVID Risk Assessment Form

Note – For participants whose initial note screening suggests increased risk to self/others, the research worker should seek supervision to confirm the risk management plan, liaise with the clinical team and document in the clinical notes where necessary.

Remote informed consent

The research worker should offer the following options for gaining informed consent:

- Written – this will involve the research worker sending 2x copies of the consent form to the individual via the post with a stamped-addressed envelope to be returned. The consent forms should be signed by the individual during the consent/screening meeting and posted back to the research worker. Upon receipt of the consent form, the research worker should sign it and scan a copy to send to the individual via email or post for their own records.
- Online - this will involve the research worker sending a link via email to the online consent form (hosted on Qualtrics) and the individual electronically signing it to provide consent to the trial.
- Verbal (recorded) – this will involve the research worker sending a copy of the consent form (either electronically or via the post) to the individual and then asking the individual to provide verbal consent to each item on the consent form. The research worker will make a recording of the verbal consent and store this securely on the secure Trust drive.

Completing the eligibility screening measures

The research worker should provide the individual with the Screening Response Pack via email or post prior to the meeting. Alternatively, depending on the modality of the meeting, the research worker could also offer the individual an option for viewing the Screening Response Pack via screen share from the research worker's computer.

The research worker, should in the first instance, print off an eligibility screening pack and record the participant's responses directly onto the physical paper versions of the measures. No patient identifiable information should be included, only the participant's trial ID. Where it is not possible to complete a physical copy, the research worker should record the participant's responses into the electronic versions of the measures hosted on the online survey platform Qualtrics.

Note - Where it is not possible to have an adapted face to face, virtual or telephone meeting, the research worker should inform the individual their referral will be placed on hold. The research worker should arrange to contact the individual to review the situation and options available (for example when physical distancing restrictions are eased, local Trust policy changes or an individual's risk status changes). The research worker should clearly document this on the Recruitment Spreadsheet and inform the clinical team of the plan.

6.4 Participant assessments

As above, the participant should be offered a choice, where possible, from the options below:

- A face to face (adapted) meeting
- A virtual meeting (conducted via Microsoft Teams or alternative video conferencing platform approved by the Trust)
- A telephone meeting

Please see the detailed procedure for each option in the section above.
Included below are any variations from the procedures outlined previously:

Face to face (adapted)

- The Assessment Response Pack should be used, as opposed to the Screening Response Pack. This should again be cleaned prior to and following all meetings with disinfectant wipes

Virtual (video) & telephone meetings

- Again the research worker should follow the Remote Assessment Checklist to discuss and problem solve setting up the remote meetings
- The Assessment Response Pack should be provided prior to the assessment/or via screen sharing, as opposed to the Screening Response Pack.
- Alternatives to providing cash honoraria should be provided, such as:
    - online Amazon e-vouchers which can be emailed to participants
    - Postal order
    - Bank transfer (where applicable)

Note – The research worker must ensure the COVID Context Questionnaire is completed for each participant assessment, at each time point.
If it is not possible to arrange an assessment via these means, the research worker should try to problem solve with the participant a way to facilitate the completion of the assessment measures. For example, to reduce the assessment battery to the core outcome measures only or to send some self-report measures in the post/via email/via online survey platform (Qualtrics) to reduce the length of assessment needing to be conducted remotely. The research worker should seek supervision from the site PI and/or trial coordinators in this instance.
Should there be no solution, the research worker should:

- Clearly document the reason for missing data in the Assessment Data Spreadsheet
- Make a plan with the participant to contact them at the next assessment point
- Update the participant's clinical team.

6.5 Therapy delivery

Due to COVID, the trial will be forced to deliver the intervention under rapidly changing circumstances. Face to face meetings will need to be adapted to adhere to national physical distancing restrictions and local Trust policy. It is also probable that for a proportion of the participants randomised to the therapy arm, therapy sessions will have to be delivered remotely in part, or entirely. The therapist should continue to deliver the intervention in line with the treatment manual with the following adaptions:

Face to face (adapted)

- Prior to the commencement of adapted face to face sessions, the therapist should revisit the COVID Information Leaflet with the participant, explaining which adaptations will be employed for their safety.
- The therapist should offer the participant time to ask any questions they may have and provide reassurance as to the importance of their safety.
- The therapist should explore which venue would be most appropriate to conduct the meeting (Trust premises, individual's home, an outside space such as a garden or public area)
- The therapist and participant should contract that if the participant experiences any symptoms of illness they contact the therapist via text or phone to arrange for the session to take place remotely
    - If the participant is too poorly, the therapist should agree an appropriate plan regarding when to reinstate sessions.
    - The therapist should inform the therapy supervisor of such an occurrence and complete relevant adverse event documentation (see SOP X Adverse Events)
- The therapist should employ physical distancing
- The therapist should avoid any physical contact with the individual
- The therapist (and wherever possible the individual) should employ the use of PPE (such as face masks/coverings, visor, gloves)
- The therapist should wash their hands/use alcohol gel prior to and following all meetings
- The therapist should clean the surfaces in the room prior to and following the session

Virtual (video) & telephone meetings

Prior to commencing remote therapy sessions, the therapist should arrange a preparatory meeting via video conference or telephone to cover essential set up and problem solving. The preparatory meeting is not a therapy session, and will need to be delivered in addition to the schedule of therapy. If the therapist has not yet met the participant, and is initiating therapy remotely, the therapist should verify the participant's identify first.
The therapist should follow the Remote Therapy Checklist to discuss and problem solve setting up the remote meetings.

Note - see ***6.3 Participant recruitment; Virtual (video) & telephone meetings*** *for further details on preparing for remote contact with participants.*
Broadly, the therapist should cover:

1. Practicalities of remote sessions, ensuring the participant has:
    - Sufficient data/internet access/Wi-Fi or reception for good connection
    - Knowledge of how to use the agreed technology (the therapist supporting the participant to build such knowledge if necessary)
    - A confidential environment for the session(s) to take place to ensure the participant can speak openly.
    - A quiet environment ideally with little risk of interruption. The therapist may need to support the participant in boundary setting within their home environment if required
2. Contingency planning for technical problems or sudden loss of connection
    - Having a clear plan in place regarding whom will do what and when in the event of problems with the connection during the session.
    - To agree an alternative option continuing the session if the primary connection fails
3. Agreeing a remote risk management plan
    - See SOP 4 Risk and disclosure for further guidance. Broadly however this would include:
        - Collaboratively discussing and agreeing a plan for what the participant and therapist will do if the participant becomes distressed during the meeting. This must include a plan around what the therapist will do if the participant becomes distressed and terminates the call and the therapist cannot re-establish contact.
    - Briefly documenting the plan (brief bullet point summary)

Note – The therapist must ensure the Therapy Fidelity Checklist is completed for each therapy session capturing the mode of therapy delivery.
If it is not possible to arrange a therapy session via these means, the therapist should try to problem solve with the participant an alternative way to facilitate the therapy sessions wherever possible, in line with national physical distancing guidelines and local Trust Policy. The therapist should seek supervision from the therapy supervisor, PI and/or trial coordinators in this instance.
Should there be no solution, the therapist should:

- Contact the site PI and therapy supervisor immediately to discuss whether the case can be paused and later restarted or whether therapy must be ended prematurely (therapy drop out).
- In both cases, the therapist should immediately inform the trial coordinators of the decision and outcome
- The therapist should ensure the decision and outcome is clearly discussed with the participant
- The therapist should update the participant's clinical notes and inform the clinical team.

6.6 Supervision and Training

It is essential that supervision and training continue to be offered and attended throughout the trial. As per ***6.1 Team Meetings*** individual risk assessments, national and local guidelines should be taken into account to determine the most appropriate means of conducting supervision and essential training.

Supervision

Supervision (both 1:1 & group) should be adapted in the following ways:

- Conduct supervision sessions remotely wherever possible, using a video conferencing platform (such as Microsoft Teams or alternative secure platform in line with local policy)
- For any face to face meetings, all attendees must maintain physical distancing and employ the use of PPE (face mask).
    - All staff should be offered the option to attend remotely, with priority given to those assessed as moderate/high risk.
    - Any staff member assessed as significant risk will be supported to attend meetings remotely at all times.

Training

Training should be adapted in the following ways:

- Any face to face training should be limited to small groups (i.e. less than x number of people) in order to successfully maintain physical distancing.
- Any training delivered face to face must include either a remote access option or the ability to undertake the training independently at a later time. This may include:
    - Offering a live video feed to the training in real time, or
    - Access to a repository of the training content (video recordings, resources, manuals etc)

7. RELATED DOCUMENTS

COVD context questionnaire
COVID 19 Staff Risk assessment
COVID 19 Participant Risk assessment
COVID 19 Risk Assessment Guidance
COVID 19 Information Leaflet
Remote Assessment Checklist
Remote Therapy Checklist

Appendix 7

Study of Trauma And Recovery

Efficacy and Mechanism Evaluation (EME) funded Add-On Study Protocol

How does the STAR therapy affect the mind and bra

V1.09 31 01 2024

VERSION CONTROL DOCUMENT

PROTOCOL: Therapeutic targets for the effective psychological treatment of trauma sequelae symptoms and psychosis in patients with comorbid Schizophrenia Spectrum Disorder and Post Traumatic Stress Disorder: Psychological and neural mechanisms.

VERSION No.	DATE	DATE APPROVED BY EME	DATE APPROVED BY DMEC/TSC	DATE APPROVED BY R&D	DATE APPROVED BY REC/HRA	DATE IMPLEMENTED	COMMENTS e.g. reason for change, stage of study, status (draft or track changes visible), date sent to co-Is or participating sites, acknowledgement of receipt, etc
1.00	5/10/2020		09/10/2020				Encoding memory task changed to be presented outside the scanner (following PPI feedback); text edited to reduce overlap with STAR protocol; procedural details and ethical considerations added for purposes of ethical review
1.01	3/11/2020						Track changes from original application visible
1.02	9/11/2020						Power calculations reinstated
1.03	20/11/2020	20/11/20		11/12/20	17/12/20	22/01/21	Track changes accepted and added to STAR trial protocol as Appendix
1.04	04.02.21	27/01/21 (by email)	25/01/21 (by email)	23/02/21	23/02/21	23/02/21	Clarification added in relation to temporary closure of scanning facilities due to Covid-19 – **No longer in effect**
1.05	15/03/21	24/03/21	16/03/21	22/04/21	27/04/21	27/04/21	Option added to consent to fMRI procedures only
1.06	28/06/21						Increased participant honorarium for fMRI due to procedures lasting

							longer than anticipated; added option of doing memory encoding task only, without scanning procedures
1.07	18/08/21	07/09/21	21/09/21	24/09/21	29/09/21	05/01/22	Additional scanning site (Newcastle University)
1.08	16/08/22	26/08/22	29/08/22	13/09/22	23/09/22	26/09/22	Memory task in scanner increased by 5 minutes at 9-months follow-up timepoint to include an everyday memories comparison condition; honorarium increased for participants completing follow-up at both timepoints
1.09	31/01/24	27/02/24	20/03/24				Retrospective explanation of the exclusion of the neutral faces condition in the fMRI social threat (emotional faces) task; change in Secondary Hypothesis E3

Title
Therapeutic targets for the effective psychological treatment of trauma sequelae symptoms and psychosis in patients with comorbid Schizophrenia Spectrum Disorder and Post Traumatic Stress Disorder: Psychological and neural mechanisms.

Short title
How does the STAR therapy affect the mind and brain?

Names of Protocol contributors

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Abstract

Background: Research over the past two decades has shown a strong and consistent association between life trauma and psychosis, with strong evidence that the effect is causal. This finding raises important questions about the mechanisms linking trauma to psychotic symptoms, and has stimulated a number of ongoing clinical trials to determine whether trauma-focused psychological interventions can help psychotic patients. Identifying and measuring trauma-related mechanisms in these patients, and determining the extent to which their amelioration is necessary for effective treatment, is likely to lead to more effective interventions in the future. The STAR trial, in which 300 participants meeting the diagnostic criteria for both schizophrenia spectrum disorder (SSD) and post-traumatic stress disorder (PTSD) will be randomly assigned to Trauma-Focused Cognitive Behaviour Therapy for psychosis (TF-CBTp) in addition to Treatment As Usual (TAU) vs TAU alone, provides an ideal opportunity to do this.

Methods: We will use the Experience Sampling Method (ESM; in which participants use smartphone-based electronic diaries to record their experiences and psychological functioning at regular intervals in everyday life) and functional Magnetic Resonance Imaging (fMRI) to investigate trauma-related mechanisms, for example dysfunctional representation of traumatic memories and hypervigilance to social threat. 200 participants from the STAR trial will be recruited to ESM and 80 will be recruited to fMRI. Both ESM and fMRI will be measured prior to randomization to the STAR arms and 9 months later, corresponding with the end of therapy in the TF-CBTp group. Analyses will determine the relationship between symptoms and hypothesized psychological and neurocognitive mechanisms and whether improvement in symptoms in the treated group is associated with changes in these mechanisms.

Discussion: The proposed investigations have the potential to enhance the scientific value of the STAR trial by identifying those psychological and neurocognitive mechanisms that must change for psychological interventions to be effective in patients with psychosis who have a history of significant psychological trauma.

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Background and rationale

As detailed in the protocol for the STAR (**S**tudy of **Tra****u**ma **A**nd **R**ecovery) trial, a large volume of research over the past decade has shown that people with schizophrenia spectrum disorder (SSD) report high rates of adversity and trauma, particularly interpersonal victimisation (e.g. emotional, physical, and sexual abuse/assaults) both in childhood and adulthood, with the majority having experienced multiple traumas (75-98% of those reporting trauma [1, 2]. The prevalence rate of Post-Traumatic Stress Disorder (PTSD) in this population is approximately 15%, which is up to five times the general population rates [3]. PTSD is characterised by intrusive memories of the trauma, such as 'flashbacks', hyperarousal, and avoidance of trauma reminders, and post-traumatic symptoms in SSD patients are frequently intertwined with psychotic symptoms, such as delusions and hallucinations [4]. However, the mechanisms leading from trauma to psychosis, and those responsible for the high prevalence of PTSD in SSD patients, are not properly understood.

The STAR trial is a rater-blind, parallel arm RCT comparing an integrated therapy to address post-traumatic stress and psychosis symptoms in SSD patients - trauma-focused cognitive-behaviour therapy for psychosis (TF-CBTp) - in addition to treatment as usual (TAU) to TAU alone, across five sites. The recruitment of a large number of patients to this trial provides an opportunity to understand these mechanisms and, in particular, to understand which mechanisms are required to change in order to treat patients with comorbid psychosis and PTSD. We propose to use two methods to assess potential mechanisms in subsamples of the STAR participants prior to randomisation and as therapy is completed: the experience sampling method (ESM; a smartphone-administered electronic diary system that allows psychological process and symptoms to be monitored in daily life) and neuroimaging.

<u>Potential mechanisms linking PTSD and psychotic symptoms</u>

An influential cognitive model that attempts to integrate findings for PTSD research, proposed by Ehlers and Clark [5], argues that peritraumatic dissociation leads to the encoding of trauma memories that are fragmented, context-independent and easily cued. At the same time negative appraisals of the self ("I am inadequate") and others ("people cannot be trusted") lead to maladaptive coping behaviours (e.g., vigilance for threat, avoidance behaviour and ongoing dissociation) which, in combination, lead to persistent PTSD symptoms. This model has received substantial support from numerous studies, including longitudinal studies of individuals first examined immediately after experiencing trauma (e.g., [6]).

It seems likely that the same mechanisms – the intrusion of dysfunctionally encoded memories, dissociation, negative appraisals and hypervigilance - are responsible for the development of PTSD symptoms in patients with a diagnosis of SSD [7]. However, the evidence that traumatic experience plays a role in schizophrenia spectrum conditions in general (and not only those patients who also experience PTSD), together with the evidence that the onset of PTSD in dual diagnosis patients often precedes the onset of psychosis [8], raises the possibility that these mechanism contribute more directly to positive symptoms of psychosis, such as hallucinations and delusions [4].In fact, there is considerable evidence for this, especially in the case of dissociation and dysfunctional cognitions (for a recent review, see [9]).

For example, the applicants have shown that the hallucinations of psychotic patients often involve trauma-related themes [10], implying that their content can be influenced by intrusive imagery relating to past adverse experiences [4].

We have also shown that dissociative experiences mediate statistically between traumatic childhood experiences and hallucinatory experiences [11] (a finding that has been replicated elsewhere e.g. [12] and confirmed by meta-analysis [13]). Using ESM we have shown that, in the daily life of patients, episodes of hallucination are often preceded by dissociative experiences [14]. Freeman and colleagues [15] found that, in people who had experienced a physical assault, peritraumatic dissociation predicted hallucinatory experiences six months later. The same researchers showed that negative appraisals also predicted hallucinations at follow-up. In the same sample, negative appraisals also predicted future paranoid symptoms [16].

Aims and objectives

Our overall objective is to test whether TF-CBTp in the STAR trial affects the mechanisms outlined above. If effective, TF-CBTp should bring about changes in these mechanisms and these changes should predict therapeutic response. This additional scientific study is essential for the future development of psychological interventions for psychosis because:

(i) *If it is true* that the amelioration of one or more of these mechanisms is required for effective reduction of PTSD symptoms by TF-CBTp, it follows that therapists can be confident in the use of this intervention with SSD-PTSD patients, and that future developments and enhancements of this therapy should be targeted at the relevant mechanisms with the aim of maximizing this effect.

(ii) *If it is true* that these mechanisms form part of the causal pathway that leads to the occurrence of positive psychotic symptoms, then it follows that trauma-focused interventions are likely to be effective not only in reducing PTSD symptoms in patients who meet the dual diagnosis criteria for SSD and PTSD, but also for reducing psychotic symptoms in these patients and also the much wider group of schizophrenia spectrum patients who do not meet PTSD criteria but nonetheless have a trauma history.

Conversely:

(iii) *If it is* ***not*** *true* that the amelioration of mechanisms is required for effective amelioration of PTSD symptoms by TF-CBTp then, if TF-CBTp is effective, other mechanisms will have to be identified to account for its effectiveness in order for the treatment to be enhanced in future research.

(iv) *If it is* ***not*** *true* that these mechanisms form part of the causal pathway that leads to the activation of positive psychotic symptoms, then alternative mechanisms will have to be identified to explain the association between traumatic experiences and psychosis.

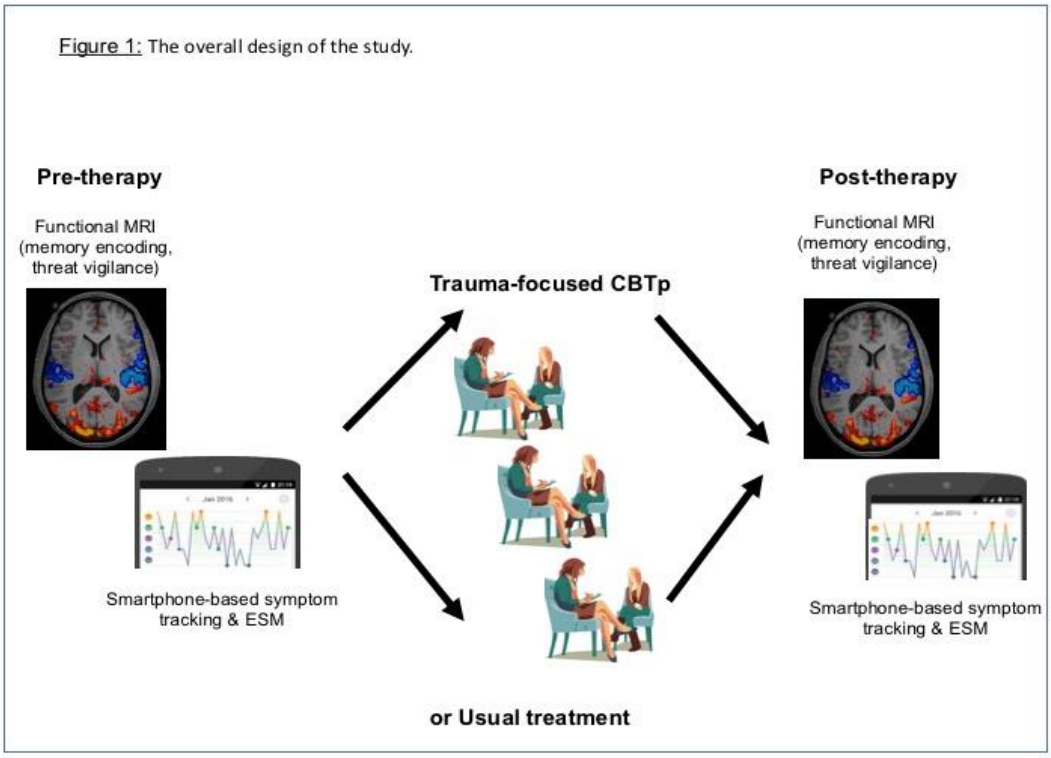
Research plan and methods: General approach

This study will be a longitudinal parallel-group design with psychological (experience sampling) and neuroimaging (fMRI) measures taken at two time points corresponding in the TF-CBTp group to pre-randomisation and end of treatment (see Figure 1).

The participants in the study will be patients meeting dual diagnosis criteria for SSD-PTSD, recruited to the STAR trial (NIHR HTA Reference: NIHR128623).

Assessments will be conducted prior to randomisation and at 9m follow-up which, in the treated group, will coincide with the end of treatment. Hence, the design will allow us to meet our objectives by testing hypotheses about changes in the psychological and neuropsychological processes that result from treatment, while at the same time examining the relationship between involuntary recall of traumatic events and the experience of positive symptoms of psychosis.

The experience sampling protocol we will use to assess changes in psychological processes will be administered to all participants who consent to this sub-study at all five trial sites (South London and Maudsley (SLaM); Greater Manchester Mental Health (GMMH); Cumbria, Northumberland, Tyne and Wear; Oxford Health; Sussex Partnership Foundation NHS Trusts). The neuroimaging assessments will be conducted at three of the collaborating centres, the University of Manchester, King's College London (KCL) and Newcastle University using compatible 3-T scanners that are calibrated across centres. For this element of the study, we will primarily aim to recruit participants from the three nearest trial sites (SLaM; GMMH, CNTW) but, if required in order to meet our recruitment targets, we will have the capacity to recruit participants who are willing to travel from other trial sites (our research costs have been calculated on the assumption that up to 1/3rd of neuroimaging participants will travel from other sites).



The experience sampling method (ESM) and its applicability to psychosis

An important limitation of traditional psychological measures is that they are laboratory-based and typically administered at a single time point. Hence they fail to assess psychological functions in the real life environment and are insensitive to how these functions are affected by contextual factors, such as specific activities the individual is engaged in, the presence of other people or stress. ESM overcomes these limitations by allowing brief psychological assessments to be administered multiple times in a day over several days and in different contexts. This is achieved by using beeps from an electronic device such as a phone app or electronic watch to prompt completion of assessments (usually in the form of a diary or very brief psychological test), which is usually designed to take < 2 minutes per assessment [17].

ESM questions can be of two kinds: those requiring the individual to report their immediate experiences and those asking them to report experiences since the previous beep. It is also possible to include other kinds of brief psychological assessments, such as making judgements about stimuli such as faces. ESM is highly tolerant of missing data [18]. The analysis method therefore does not require a valid assessment to be completed at each beep; typically participants are included in analyses if 20/60 valid reports are recorded over a six day assessment period. This threshold results in high compliance/inclusion rates, even with repeated time points e.g., pre and post-therapy [19]. Therefore, it is a practical and well-tolerated methodology.

Despite its apparent complexity, ESM has been widely used in mental health research, and has been employed in many studies with patients with psychosis over a period of more than two decades [20]. The present applicants have used it in previous studies with patients suffering from severe mental illness that have measured many of the variables of interest in our proposed study such as hallucinations, paranoid beliefs and dissociative experiences [14, 21] [22] [23] [24].

Neuroimaging and its potential for identifying treatment mechanisms

Recent research has harnessed functional neuroimaging to probe the mechanisms of psychological therapies [25, 26]. The field is expanding rapidly – across disorders, there are now over a hundred publications, with over half of these being published in the last three years. These studies have almost exclusively been conducted in mood and anxiety disorders, with only a handful in relation to PTSD [27-29] and even fewer in psychosis [30-32]. To date, our group is the only one to have employed these methods in patients with SSD receiving cognitive behaviour therapy tailored to psychosis (CBTp) (see Figure 2). These studies have demonstrated that functional neuroimaging can be used to better pinpoint mechanisms of therapeutic change [32-34] and can also be used to predict who will respond to treatment [35, 36].

Research on the neurobiology of PTSD points to ways of using neuroimaging to probe the mechanisms of action of TF-CBTp. According to psychological models of PTSD, traumatic memory intrusions occur because the memory is in a 'raw' and incompletely processed form, lacking temporal and contextual detail, which prevents the memory from being stored per typical memory episodes. Trauma-focused psychological therapies are posited to reprocess trauma memories to consolidate the memory in a more complete representation, by updating it with accurate information and meta-memory characteristics; for example, with chronological and contextual information [37].The neurobiology underlying this potential mechanism has only recently received attention. However, disrupted hippocampal memory encoding of the context surrounding traumatic events has been identified as a likely mechanism underlying PTSD [38, 39], a model that draws on evidence that the hippocampus acts as a point of convergence that binds together multi-modal information into a single coherent representation [39, 40].

Practical and ethical reasons make it impossible to examine the live encoding of a real-life traumatic event. Therefore, fMRI studies typically employ negative, emotionally arousing visual stimuli as trauma analogues (see [41]). When encoding trauma analogue items, there was elevated amygdala activity which boosted subsequent memory for these items [42, 43]. However, memory for the associations between trauma analogue items and neutral visual stimuli that were present during encoding was impaired, and the level of this impairment was predicted by the reduction in hippocampal activity during encoding [42]. Moreover, these studies have shown that a 'post-encoding period' shortly after encoding the trauma analogue items is a key marker for the formation of trauma memories, and that amygdala-hippocampal activity predicts subsequent

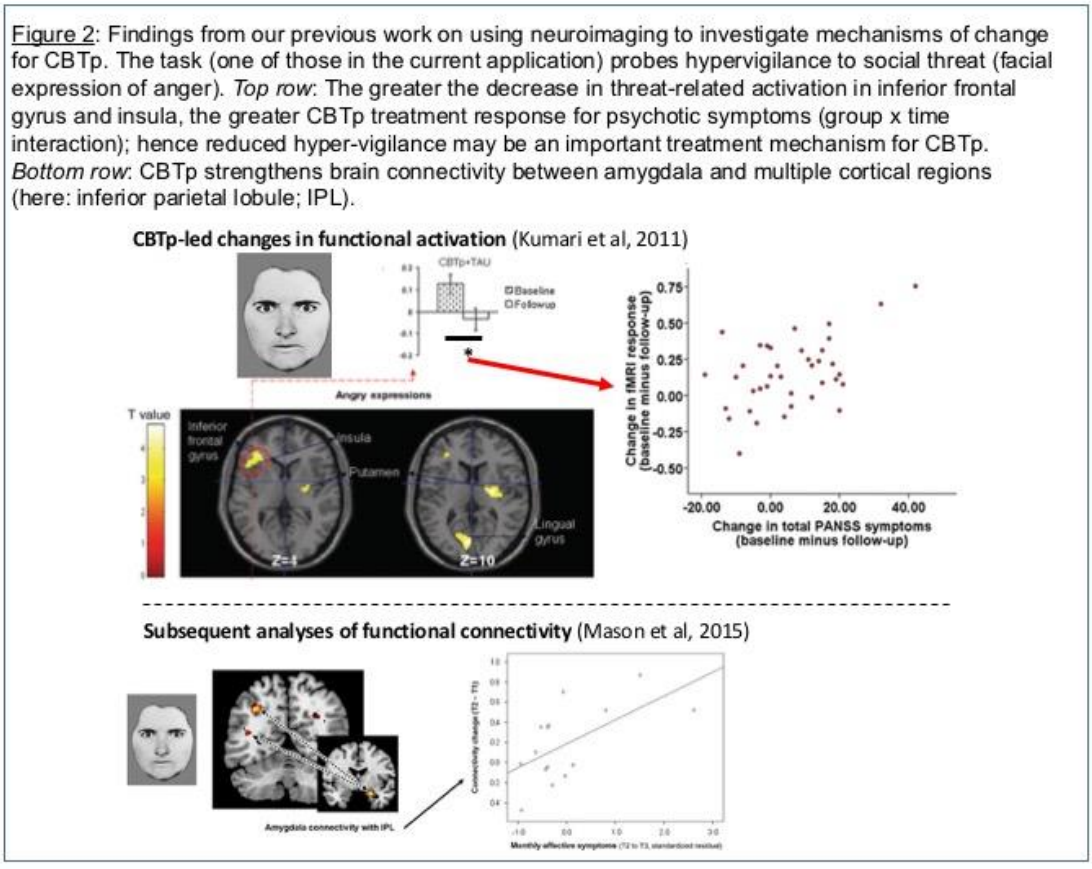


Figure 2: Findings from our previous work on using neuroimaging to investigate mechanisms of change for CBTp. The task (one of those in the current application) probes hypervigilance to social threat (facial expression of anger). *Top row*: The greater the decrease in threat-related activation in inferior frontal gyrus and insula, the greater CBTp treatment response for psychotic symptoms (group x time interaction); hence reduced hyper-vigilance may be an important treatment mechanism for CBTp. *Bottom row*: CBTp strengthens brain connectivity between amygdala and multiple cortical regions (here: inferior parietal lobule; IPL).

memory bias [43, 44] and level of intrusions experienced on subsequent days (Bisby et al, in preparation) relevant to our hypotheses linking the neuroimaging data to the ESM data.

Specific hypotheses

Based on previous findings, we have a series of hypotheses that we will test using both ESM and in fMRI in STAR trial participants who are willing to undertake the additional protocols, as listed in Table 1 overleaf.

Participants

Participants will be those recruited to the STAR trial and who consent to participate in these additional research procedures. There are no additional exclusion criteria, apart from clinical contra-indications to participating in the fMRI part of the study, which include having received any metal injuries to the eye, had metallic objects (including clips) inserted into the body at an operation, having received a shotgun injury, or having a heart pacemaker.

Sample size calculations

ESM: We will recruit 200 participants across five sites (a total of 40 per site), which corresponds to two-thirds of the full STAR trial sample (N=300). We predict that we will have a 25% attrition rate from the ESM study, which will provide a final sample of approximately n=75 per group completing both of the ESM measurements (i.e., pre- and post- therapy), assuming equal participation across groups. These targets and attrition rates are in line with previous studies using ESM to assess changes in CBTp [19].

For hypothesis E1, a total of 150 participants will be needed to provide 85% power for our therapy vs. control group comparisons. Due to the complexity of sample size estimation for three-level models (which require an unfeasibly large number of unknown parameters to input), the sample size calculation is based on a simple (two-level) multilevel model with random intercepts at the subject level and autocorrelated residuals with an autoregressive structure of the first order at the ESM-beep level. We assume following input parameters: 40 completed data points on average per participant (out of a possible 60), with a standard deviation of 2 for each group, an autocorrelation of 0.3, an intra-cluster correlation of 0.1 and a mean difference of 0.4 (on a 1-7 Likert scale measuring the construct) to be detected at the 0.05 level of significance.

Hypothesis E2, E3 and E4 will use the beep level measures to assess prediction of clinical outcomes (E2) and mediation between the beep level measures themselves. Assuming 40 data points per participant over the two time periods, gives approximately 14,000 unique data points (350 participants at both time points x 40 data points). Although these are not independent data points, the effective sample size will have over 95% power to detect standardised associations between beeps as small as 0.1, and close to 100% power for standardised associations above 0.3.

fMRI: We will recruit 80 participants from the STAR trial, to allow for 25% attrition and allow for a final sample of approximately n=30 per group completing both of the fMRI measurements (i.e., pre- and post- therapy), assuming equal participation across groups. These target and attrition rates are both in line with our previous longitudinal fMRI case-controlled study probing changes following conventional CBTp. Most of these patients will be recruited from the Greater Manchester Mental Health, Cumbria, Northumberland, Tyne and Wear, and South London and Maudsley NHS sites closest to the scanners, but we are assuming that up to a third will travel from other sites; hence we will need to recruit a minimum of 26 participants at each of the two close sites (43% of those potentially available).

At 80% power, we would be able to detect a small effect size of $d \geq 0.37$ in Hypotheses N1a and N1b (group x interaction in fMRI measurements). At 80% power, we could also detect a moderate-sized correlation ($r \geq .43$) between change in fMRI activation and 1) symptom improvement (Hypotheses N1 and N2) and 2) the experience sampling measures (Hypotheses NE1 and NE2).

We anticipate both effects to be larger, based on our past work. Whilst no studies have yet examined change in trauma memory representations following TF-CBTp (Hypothesis N1a), we have previously demonstrated the hypervigilance task used to test Hypothesis N1b is sensitive to

conventional CBTp-led changes in fMRI activation and that the effect size was large in the regions we had predictions for (d = 1.17) [31]. We will have 99.9% power to detect this sized effect with our projected sample size. In addition, we have previously shown that the correlation between CBTp-led changes in fMRI activation and improvement in psychotic symptoms was of large effect size [$r(22)=0.55$] [32]. We would have 90.3% power to detect this sized effect with our projected sample size, and could still detect this sized effect at 80% power even if the final sample size is significantly smaller (N=19).

Recruitment and consent process

The STAR protocol asks participants to consent to be approached about further add-on studies related to the trial. If that consent is given, and once the participant has agreed to take part in the STAR trial, fully informed consent will be sought for the current study. Participants will be able to consent to either or both the ESM and the MRI protocols, or they may refuse consent to both but remain in the STAR trial. Consent for the fMRI protocol will include participants' consent for a summary of their trauma memory assessment to be used to generate stimuli for the fMRI experiment, to avoid burden from repeating this assessment. For the fMRI study there will also be the option of consenting to participating in the memory encoding task only, which is done outside the scanner. All consent process and related materials (PIS and consent forms) will be approved by our service user reference group.

The procedures we will use will fully inform participants of their options with no pressure whatsoever to take part in these additional protocols, with the primary objective of maintaining the integrity of the STAR trial.

<u>Renumeration/compensation</u>

Remuneration for participants' time to complete 6 days of ESM will be £30 at each time point, with an extra £15 for participants who complete both timepoints (i.e., £75 in total). It will be £60 for fMRI procedures at each time point, with an extra £30 for participants who complete both timepoints (£150 in total). Participants choosing to complete the memory encoding task only, without the scanning component, will be remunerated £15 at each time point (£30 in total).

Table 1: Primary hypotheses. Testing these will allow us to achieve our primary objective of determining whether changes in specific psychological mechanisms are required for the efficacy of TF-CBTp.

Hypothesis	**Level and prediction** (E=ESM hypotheses; N=neuroimaging hypotheses)	**Justification**
TF-CBTp will lead to reductions in intrusive trauma memories and related psychopathology	**At symptom level (E1):** The treatment group, compared to the controls, will experience greater reductions in intrusive trauma memories, negative appraisals, avoidance, dissociation and vigilance for threat.	Past research on PTSD shows that these processes play a causal role in PTSD symptomatology and that effective psychological interventions ameliorate these processes, but this has not yet been shown in patients with psychosis. We therefore hypothesize that TF-CBTp must change these mechanisms to be effective.
	At neural level (N1a): The treatment group will show reduced dysfunctional representation of trauma memories as measured by neuroimaging	Dysfunctional representation of trauma memory (increased amygdala and insular activity but reduced hippocampal activity) is the neural mechanism underlying the maladaptive storage of intrusive trauma memories. Hence, if the treatment leads to less dysfunctional memory representations, we should see enhanced hippocampal activity and reduced amygdala and insular activity when retrieving trauma memories.
	At neural level (N1b): The treatment group will show reduced hypervigilance for potential sources of social threat, again measured by neuroimaging	Hypervigilance for threat is a symptom of PTSD. A neural correlate is amygdala response to social threat stimuli. Hence, we will test whether there is a reduction in this amygdala response that is specific to those receiving treatment.
The above reductions in intrusive trauma memories and related psychopathology will correlate with the level of symptom	**At symptom level (E2):** Changes (between time 1 and time 2) in the experience sampling measures of trauma memory, negative appraisals, avoidance, dissociation and hypervigilance will predict reductions in PTSD symptoms	If these mechanisms are responsible for PTSD symptoms, and if the treatment changes them, then the extent of change should predict the extent to which patients' PTSD symptoms improve.

improvement that patients experience following TF-CBTp	**At neural level (N2):** Changes (between time 1 and time 2) in neuroimaging measures of memory representations and hypervigilance should predict reductions in PTSD symptoms	If these mechanisms are responsible for PTSD symptoms, changes in the neural correlates of these processes should also predict the extent to which patients' PTSD symptoms improve.

Secondary hypotheses. Testing these will meet our broader objective of determining whether trauma-related psychological mechanisms play a causal role in the occurrence of psychotic symptoms

Hypothesis	**Level and prediction** (NE=hypotheses relating to relationships between neuroimaging and ESM)	**Justification**
Measures at the neural level will predict symptom level measures	**Between neural and symptom level (NE1):** At each time point, neural responses measured by fMRI during encoding and recall of trauma memories will predict the frequency and distress of trauma memories in daily life, measured during experience sampling	We have hypothesized specific neural mechanisms associated with intrusive trauma memories (see N1a above). These mechanisms, measured in the scanner, should therefore predict the actual occurrence of intrusive trauma memories in the daily lives of patients, as measured by ESM.
	Between neural and symptom level (NE2): At each time point, neural responses measured by fMRI during a task assessing vigilance to social threat will predict levels of threat hypervigilance and paranoid experiences in daily life measured during experience sampling.	Considerable previous research shows that paranoia is associated with hypervigilance for threat. Hence, we would expect the neural correlates of hypervigilance (see N1b above) to predict hypervigilance for threat and paranoid thoughts in the daily lives of patients, as measured by ESM.
Psychotic symptoms will be mediated by trauma memory intrusions, negative appraisals, avoidance, dissociation, and hyper-vigilance for threat	**At symptom level (E3):** At each time point, the occurrence of intrusive trauma memories, negative appraisals, avoidance, dissociation and vigilance for threat[1], measured in daily life, will predict the subsequent exacerbation of psychotic symptoms (hallucinations and paranoid experiences)	Given previous evidence of the causal role of trauma in psychosis, we hypothesize that trauma memories, negative appraisals, avoidance, dissociation and vigilance for threat will trigger the onset of psychotic symptoms in daily life. We will be able to test the relative contribution of each process[1] using our ESM data.
	At symptom level (E4): At each time point, experiences of dissociation and negative appraisals will mediate between distressing involuntary recall of traumatic experiences and exacerbation of hallucinatory experiences	Given our previous finding that dissociative experiences are associated with hallucinations, and given that dissociative experiences can be triggered by trauma memories, we predict that dissociation measured in daily life will mediate between trauma memories and hallucinatory experiences.

[1] We have widened the range of processes to be tested due to recent evidence that processes other than trauma memories are relevant to the link between PTSD and psychotic symptoms (Hardy et al, 2021; Frost, 2023)

	At symptom level (E5): At each time point, negative appraisals and hypervigilance for threat will mediate between distressing involuntary recall of trauma memories and exacerbation of paranoid experiences	Similarly, if negative appraisals and hypervigilance for threat are triggered by trauma memories in daily life, these mechanisms should mediate between trauma memories and paranoid episodes in our ESM data.

Specific ESM protocol

Method of delivery and data security

ESM questions will be delivered on smartphones using an app called M-Path, an ESM app developed by Prof Myin-Germeys at KU Leuven (further information about the app can be found at https://m-path.io/landing/) which has been specifically designed for research with people suffering from severe mental illness. The app is Android and iOS compatible and we will provide participants with an Android smartphone in the event that they do not already own a suitable device.

All data collected with the m-Path app (i.e., questionnaire data) are initially stored locally in a protected folder on the smartphone of the participant which can only be accessed through the m-Path app (it cannot be accessed through other apps). To enhance data security and to prevent data leakage at all times highly secured application-layer encryption is applied. All answers given to questionnaires, all downloaded questionnaires, personal information (i.e. alias), text information, options and notes are stored on the phone using AES 256 bit-encryption with PKCS7 padding. When the user has access to a 3G/4G/5G network, data are transferred to secured university servers located in Leuven and Heverlee. These data will have no identifying data other than project ID numbers. The project team will be able to download the data from the servers on to STAR team computers via a secure and password protected portal. Once downloaded on to the project machines, the data will be encrypted and password protected. In the unlikely event of a security breach, all affected users will be notified. Ethical considerations are considered separately below.

ESM questions

We will ask participants to answer ESM questions 10 times a day over six day periods, each time lasting approximately two minutes. They will complete the ESM procedures once they have completed the main STAR trial baseline assessment, prior to randomization, and at 9th months post randomization (i.e. coinciding with the planned end of treatment in the treatment arm). Completion of the questionnaires will be cued by electronic beeps from the smartphone app on a quasi-random sequence, which will be adapted to individual participants according to their typical sleep-wake patters (e.g. the app will be programmed to notify participants only in hours when they are likely to be awake, to avoid excessive burden and inconvenience).

Our choice of ESM questions has been informed by previous studies and will be subject to piloting, rewording or omitting by the STAR experts by experience reference group, who will give final approval. Twenty-nine questions will cover the following specific topics (unless otherwise stated, responses will be rated 1 – not at all to 7 – very much so):

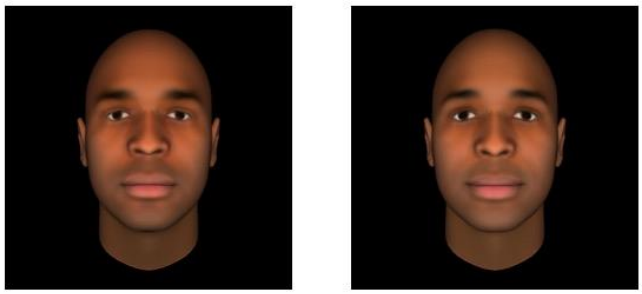
(i) mood (six questions, e.g. “Right now I feel cheerful”); (ii) negative trauma-related cognitions (three questions, e.g. “Right now I believe the world is a dangerous place”); (iii) paranoia (two questions, e.g. “Right now I feel suspicious”); (iv) hallucinations (two questions, e.g. “Right now I can hear a voice or voices that other people cannot hear”); (v) context (two questions, e.g. “Right now I am on my own/with strangers/with people I feel close to”; choose one); (vi) PTSD symptoms (eight questions, e.g. “Since the last beep unwanted memories about the experience popped into my mind”); (vii) dissociative symptoms (three questions, e.g. “Since the last beep I felt like the world around me was not real”); (vii) attachment cognitions (two questions, e.g. “Since the last beep I worried that others don’t’ really want to be close to me”); (ix) emotional impact of the assessment (one question, “This beep has disturbed me”).

In addition to these questions, we will include an experimental measure of ‘vigilance for social threat’, linked to mistrust, a key process in both PTSD and paranoia. Human beings make rapid (within a few hundred milliseconds) judgments about the trustworthiness of unfamiliar faces [45] reflecting the need to make efficient and rapid decisions about individuals we encounter in daily life - given the number of people we typically encounter, we do not have time to ‘think through’ whether each person can be trusted [46]. Recent work by one of the researchers has shown that paranoia is associated with a bias towards judging unfamiliar faces as untrustworthy [47], reflecting an implicit bias in information processing that cannot be accessed by questionnaires. We will attempt to measure this bias in everyday life.

M-path will be programmed so that, at each beep, participants will be presented with two male faces from the Princeton Social Perception laboratory trustworthiness dataset

(http://tlab.princeton.edu/databases/), which have previously been evaluated for normative ratings of trustworthiness (one face from the faces rated +1 SD in trustworthiness and one face from the -1SD faces). Within each beep, the two faces presented will be matched for ethnicity (White, Black or Asian); within each day, 50% of the beeps will be White and 50% will be BAME (Black or Asian). Participants will rate the faces on a 7-point scale of trustworthiness.

Figure 3: Untrustworthy (left) and trustworthy (right) BME faces from the Princeton Social Perception Lab.



ESM analysis plan

We will use multilevel factor analysis to confirm construct validity and factor structure of the constructs; since we will largely use questions employed in previous studies we do not anticipate problems in this regard but, if poorly fitting ESM items are identified, they will be dropped from analyses. As in previous studies, we will define exacerbations of hallucinatory episodes as one or more consecutive moments with a mean score ≥ 3 on the ESM hallucination items. Paranoid intensity at each moment will be defined in terms of mean score on the relevant items.

Multilevel models will be used to examine study hypotheses, taking into account the hierarchal structure of ESM data: beeps nested within days nested within participants. Typically for investigating constructs at the beep level, this requires a random intercept for each participant and for each day within participant to be included in the random effects.

Alternatively, for each construct at each time point, summary measures such as variability across the beeps within a participant or the intraclass correlation coefficients (ICCs) can be calculated to estimate the proportion of variability in each level of the data (i.e., assessment, day, and person levels) to be explored as outcomes in further analyses. To test Hypothesis E1 (the treatment group, compared to the control group, will experience greater reductions between time 1 and time 2 in intrusive trauma memories, negative appraisals, avoidance, dissociation and hypervigilance) we will use multilevel models to compare the treatment and control groups at the two time points, using ESM measures of the relevant mechanisms as outcome variables, and including an indicator for treatment group as a covariate, and an appropriate random effect structure.

To test Hypothesis E2 (reductions in intrusive trauma memories, negative appraisals, avoidance, dissociation and hypervigilance between time 1 and time 2 will predict reductions in clinically assessed PTSD symptoms) we will use multilevel models with PTSD symptoms as dependent variable and each of the individual constructs and treatment group as covariates, with an appropriate random effect structure to account for the repeated measures of the covariates.

To test Hypothesis E3 (the occurrence of intrusive trauma memories, negative appraisals, avoidance, dissociation and vigilance for threat, will predict the

subsequent exacerbation of psychotic symptoms i.e., hallucinations and the experience of paranoia in daily life), we will use multilevel models with each PTSD symptom score in the interval since the previous moment as the predictor variable and hallucination and paranoia scores at the moment as dependent variables, with an appropriate random effect structure.

To test Hypotheses E4 (experiences of dissociation and negative appraisals will mediate between distressing involuntary recall of traumatic experiences and exacerbation of hallucinatory experiences) and E5 (negative appraisals and hypervigilance for threat will mediate between distressing recall of traumatic experiences and exacerbation of paranoid experiences in everyday life) we will run multilevel models and use the difference in coefficients approach for mediation. This involves fitting two separate models for the outcome with and without the mediators as covariates, and an appropriate random effect structure. The difference in coefficient between these models for the distressing recall variable is a measure of the indirect effect through the respective mediators, and non-parametric bootstrapping is used to obtain a standard error for inference testing.

Specific neuroimaging/autonomic measurement protocol

The neuroimaging assessments will be conducted at three of the collaborating centres, the University of Manchester, King's College London (KCL) and Newcastle University using compatible 3-T scanners that are calibrated across centres.

During the scan, participants wear a respiration belt that measures any small changes in breathing and heart rate during the session. This is because these cause small changes to the BOLD response leading to artefacts on the fMRI images, so including these measurements during image processing improves the signal to noise ratio of task-related neural activation.

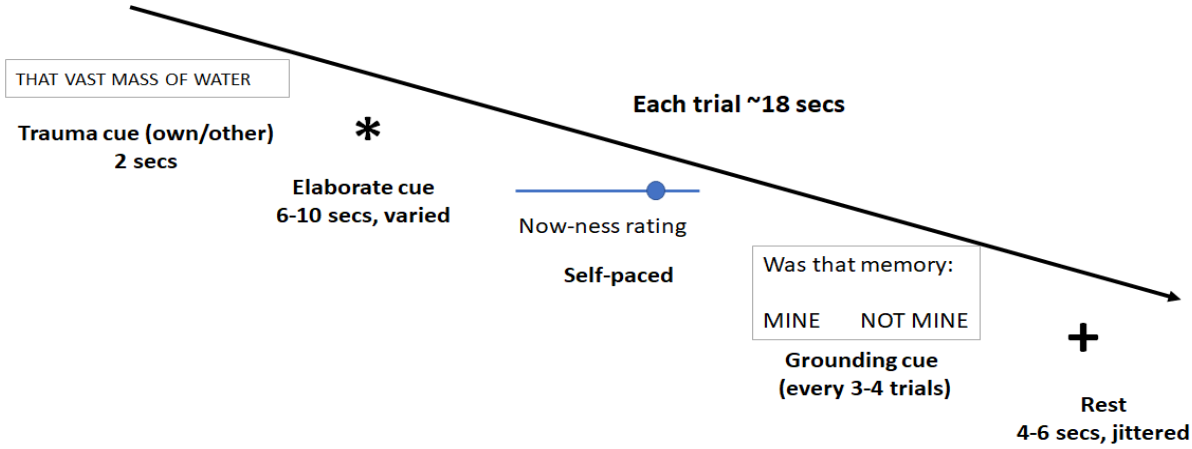
fMRI will be acquired while participants perform tasks probing: 1) retrieval of trauma memories; 2) hyper-vigilance to social threat. This will take place at the same two time points as ESM, described above. The core imaging protocol will last approximately 45 minutes and consist of a structural scan (10 minutes) plus two task-based fMRI tasks (15-20 minutes each). Participants will perform a brief practice of tasks, including a memory encoding task (10 minutes, see below), outside of the scanner, to familiarise themselves with the task instructions and button responses. During fMRI, we will ask participants to give self-report ratings of validated mood state items (happy, sad, anxious, irritable, angry, energetic) and experiences of dissociation chosen from the ESM items (e.g. "I feel spaced out, numb or emotionally shut down") [48] and include these in analyses.

<u>Neuroimaging plan and hypothesis-testing</u>

Retrieval of idiosyncratic trauma memory: *To test Hypothesis N1a* (the treatment group will show improved representation of trauma memories and greater emotional control measured by neuroimaging when prompted to think about trauma), we will examine neural responses during retrieval of the patient's idiosyncratic trauma memory using a previously validated script-driven procedure [49-51], which we will adapt to reduce the potential for patient stress. Prior to the scanning visit, patients will be asked to identify stimuli that remind them of their traumatic experience, already discussed as part of the main STAR trial baseline assessment. At the 9-months follow-up timepoint they will be asked to identify stimuli (short phrases) that remind them of a neutral, non-traumatic experience (e.g. a movie that you remember seeing in the cinema, or a journey that you used to frequently make) for a 5 minute additional comparison task. Subsequently, during the neuroimaging session, they will be visually presented with key words and phrases relating to these cues, interspersed with those from a thematically distinct trauma account generated from previously published trauma research (see Figure 4). We will identify activity that correlates with subjective ratings of 'nowness' of the trauma memory (i.e. how much the memory feels like it's happening "right now", a measure of how well the memory has been contextualised), sampled by self-report on each trial. We will also periodically ask participants to indicate whether the cue is related to their own trauma experience ("mine") or not ("not mine"), to help participants remain grounded in the here-and-now. We will ask the current study experts by experience reference group to refine this established protocol for the current study context to minimise the

potential for participant distress, and there is a separate statement on the consent form for participants to indicate whether they are happy to take part. This may entail adaptations such as dividing the task into multiple shorter blocks.

Figure 4: Idiosyncratic trauma memory trial structure.



Post-encoding rest period: At the end of the trauma memory task, brain activity is measured during rest (5 minutes). Neural activity during this window is used to establish the reconsolidation of trauma memory content, with resting state connectivity of amygdala during this 'offline' period serving as a marker for negative memory biases [43].

To test Hypothesis N1b (TF-CBTp will lead to greater reductions in hypervigilance for social threat) participants will be asked to complete a task probing the processing of facial emotions and ability to regulate their emotional responses to social threat. As per our previous studies examining neural changes following CBTp [32-34], participants are presented with faces displaying potentially threatening (angry) or affiliative (happy) emotions[2]. On half of the trials, participants will view the images and give subjective ratings of the level of threat (automatic threat processing). On the other half of trials, participants are instructed to reappraise the stimuli to a more neutral explanation (e.g., "the person is angry with someone else, rather than with me"; reappraised threat). Neural activation during automatic processing of potentially threatening emotion will be contrasted against activity when threat is reappraised as neutral.

To test Hypotheses NE1 and NE2 we will combine the ESM and neuroimaging data to test our prediction that these neural changes are associated with changes in the relevant psychological processes in everyday life. We will also use the clinical data collected in the STAR trial to test the corollary, that the TF-CBTp-led changes in activation are related to the level of improvement in PTSD symptoms.

All neuroimaging analysis will be undertaken using Statistical Parametric Mapping (SPM). To determine effects of treatment on neuronal responses to tasks in hypothesized regions of interest, we will perform repeated measures Analyses of Variance (ANOVAs) to identify significant interactions, with treatment (TF-CBTp vs usual treatment) and time (post vs pre) as between and within-participants variables respectively. To relate neuroimaging findings to ESM and clinical

[2] It became clear at the piloting stage with the Expert by Experience reference group that the full fMRI procedures took well over an hour, and the group fed back this task was not feasible for inclusion in the scanner in its entirety as it was too long, laborious and time-pressured to present all of the stimuli in the limited amount of scanner time available. This would have been uncomfortable for our clinical population and would have had scanning cost implications. The task was therefore shortened by removing the neutral faces trials, which was the least informative condition. There is emerging consensus that "neutral" facial emotions can be misinterpreted as threatening by psychosis population (Underwood et al, 2015), so there was scientific justification for removing the neutral condition, rather than the reappraised threat condition, which is a better measure of 'neutral' (i.e., non-threatening) emotion (Fitzgerald et al, 2020).

variables, we will perform correlations between signal in significant regions of interest and the ESM and clinical measures.

Memory encoding task (outside of scanner)*:* To measure memory abilities, we have adapted an established task [42] to be significantly briefer (10 mins). Participants encode target memory items (pictures) that are each presented alongside either a negative image (e.g. spider, crashed car) or neutral image (e.g. chair, banana)**.** *Retrieval:* Participants complete a retrieval test (5 mins, also outside of the scanner), consisting of previously seen images (66%) and new images (33%) which they asked whether they have seen before or not, to measure memory accuracy.

Acceptability and ethical considerations

All of our tasks have been or will be piloted with our experts by experience reference group to ensure acceptability and user-friendliness of our procedures. Specifically, feedback will be elicited with regards to content of ESM items, to trauma memory words for the fMRI task, and to the photographs used for the memory task.

ESM is a method that has been widely used in research with patients suffering from psychosis, beginning in the 1990s; a search in Google scholar with the search terms 'ESM' and 'psychosis' led to 1,890 hits. Several features of the method make it highly tolerable. First, the assessments are designed to be very brief (typically < 2 minutes per administration); second, participants can miss completing assessments and are told that they should do so if completing them interferes with ongoing activity (e.g. when driving).

We have considerable experience with this methodology. One of the applicants, Varese, has recently published an edited book on ESM methodology [52]; another, Emsley, has extensive experience of analysing ESM studies and wrote the chapter on the statistical analysis of ESM data in Varese's book; another, co-CI Bentall, has published ESM studies of paranoid symptoms [21] and auditory hallucinations [14]. The method has recently been adapted for use in clinical trials [19]; 116 patients with psychosis) and is proving to be acceptable in the ongoing ReProcess trial of trauma-focussed therapies for patients with a dual diagnosis of schizophrenia and PTSD (the same group of patients we will be studying) that is currently being conducted in the Netherlands (ISRCTN56150327), on which applicant Hardy is a co-applicant; of the 29 people recruited to that trial so far (trial sample aim is 200), all have consented to participate in the ESM protocol. Hence we believe that the acceptability of ESM has been demonstrated in precisely the circumstances in which we propose to employ it.

Neuroimaging is more demanding for participants because it involves a longer time commitment from participants (4 hours in total on two occasions: approximately 1.5 hours eliciting and rating trauma reminder stimuli prior to scanning visits, then around 2.5 hours per visit, with approximately 1 hour in the scanner itself (45 minutes of scanning, 15 minutes to settle in and out of scanner), 1 hour to do safety checks with the radiographer, receive instructions, practice tasks, and 30 minutes for debrief and feedback). People will be able to choose not to take part in the scanning, and complete the memory encoding task only, if they think they would find the scanner environment uncomfortable or claustrophobic. However, we know of no evidence that psychotic patients are less able to tolerate the scanner environment and numerous (many hundreds) studies have conducted neuroimaging with this patient group over a period of thirty years, including studies led by Co-PI Peters and Co-I Mason in a similar investigation of the mechanisms of action of CBTp [31, 32. 34]. The locations where the neuroimaging will take place have excellent track records for acceptability to patients experiencing psychosis. We use a "mock scanner" environment prior to scanning to help with acclimation, and we typically achieve well over 80% revisits of our patient populations.

Neuroimaging has been increasingly used to investigate processes involved in therapeutic change. Across disorders, there are now over a hundred such publications. In our studies investigating the mechanisms of change in psychotic patients receiving cognitive-behaviour therapy [32-34] we found no evidence that imaging impacted on recruitment or retention into the main intervention being evaluated. Nonetheless, we recognise the importance of taking steps to reduce the probability of adverse reactions to our neuroimaging protocol that would affect participation in the STAR trial. First, as with our previous studies, participation in the neuroimaging

protocol will be entirely voluntary and all potential participants will be made aware that they can decline to take part if they anticipate that it will be stressful; it is for this reason that we are seeking to recruit only a subsample of STAR participants into the neuroimaging study (n=80 out of a possible 300). Second, we are utilising protocols previously used successfully with PTSD patients [50, 51] which we have modified to ensure it is briefer, and less arousing for our patients. Finally, of course, participants will be free to terminate the scanning sessions any time they wish without affecting their involvement in other aspects of the trial.

We will elicit feedback from participants on their experience of taking part in the study to ensure acceptability throughout, with a view to adapting our research procedures should concerns arise or barriers be identified. We will have the same standard protocol as the STAR trial for managing any distress potentially elicited by the study procedures, which has been developed in collaboration with experts-by-experience. This will include a debrief at the end of the scanning procedures with the RWs to enable participants to feedback any potential distress, and to 'take a breather' before leaving the scanning facility. We will also offer telephone contact within 48 hours of completing the study procedures to check on participant well-being, and a summary of support and crisis numbers. All appointed RWs will have a psychology background and have experience of working with populations with severe mental health problems. They will receive training in interviewing skills and how to respond sensitively and empathically to any distress that arises. There will be close supervision of RWs throughout the trial (by experienced Research Clinical Psychologists) and regular review both within the main trial team (at monthly meetings) and at the TSC and DMEC.

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