Trial Title: Does a Phased Approach Enhance Outcomes for Trauma-Focused Cognitive Therapy for Complex Posttraumatic Stress Disorder (CPTSD)?

Internal Reference Number(s): B22/21 Short title: PHASE-CPTSD

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Chief Investigators:

Dr Michael Duffy, School of Social Sciences, Education and Social Work, The Queen's University of Belfast

Professor Anke Ehlers, Department of Experimental Psychology, University of Oxford

Co-Investigators:

Dr Deborah Lee, BerkshireTraumatic Stress & South Central Veteran Mental Health Services, Berkshire NHS Foundation Trust

Professor Ly-Mee Yu, Nuffield Departmentof Primary Care Health Sciences, University of Oxford

Professor Apostolos Tsiachristas, Nuffield Department of Population Health, University of Oxford

Dr Ciaran Mulholland, School of Medicine, The Queen's University of Belfast

Dr Hannah Murray, Department of Experimental Psychology, University of Oxford

Dr Nick Grey, Psychology and Psychological Therapies, Sussex Partnership NHS FoundationTrust

Dr Kevin Dyer, Psychological Services, The Queen's University of Belfast

Mr Robin Kelly, North Belfast Day Center, Belfast Health and Social Care Trust

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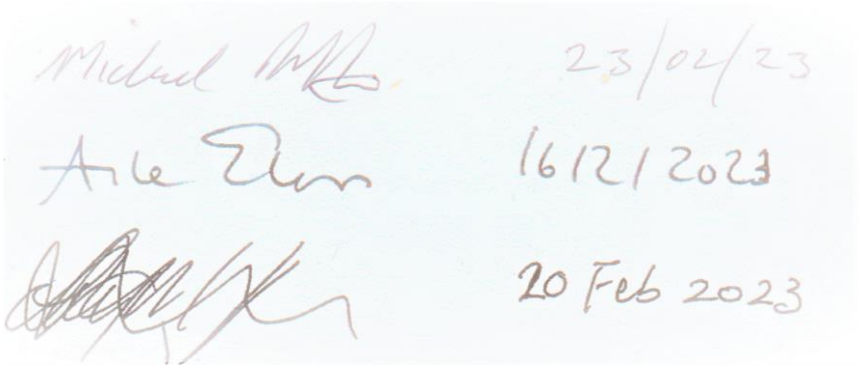
Chief Investigators' Signatures:



Statistician Signature:

Declarations of Conflict of Interest: Anke Ehlers and her team have developed trauma-focused Cognitive Therapy for PTSD (CT-PTSD). Deborah Lee has developed the Compassion Resilience focused therapy and training used in the stabilisation phase of the phased CT-PTSD treatment to be investigated in this project.

Several of the applicants occasionally give paid workshops on these treatments. However, training materials, a therapist guide and videos on CT-PTSD are also available free of charge at https://oxcadatresources.com.

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1. KEY TRIAL CONTACTS

Chief Investigators	Dr Michael Duffy School of Social Sciences, Education and Social Work The Queen's University of Belfast Room 02.004 - 69 University Street United Kingdom BT7 1HL Email: michael.duffy@qub.ac.uk T: +44 (0)28 9097 3298 Professor Anke Ehlers Centre for Anxiety Disorders and Trauma Department of Experimental Psychology University of Oxford The Old Rectory Paradise Square Oxford OX1 1TW Email: anke.ehlers@psy.ox.ac.uk T: 01865 618600
Sponsor	Queen's University of Belfast Sponsor's Rep.: Kathryn Taylor Research Governance Manager Research & Enterprise Directorate 63 University Road Belfast BT7 1NN Email: k.taylor@qub.ac.uk T: +44 (0)28 9097 3861
Clinical Trials Unit	Nuffield Department of Primary Care Health Sciences, University of Oxford 1st Floor, Gibson Building Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG Tel: 01865 617199
Lead Statistician	Professor Ly-Mee YU, DPhil Lead Trial Statistician Deputy Director Academic Primary Care Clinical Trials Unit Radcliffe Primary Care Building Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG Tel: 01865 617855 Email: ly-mee.yu@phc.ox.ac.uk
Health Economics Lead	Professor Apostolos Tsiachristas Nuffield Department of Population Health University of Oxford

	University of Oxford Richard Doll Building Old Road Campus Headington Oxford OX3 7LF Email: apostolos.tsiachristas@ndph.ox.ac.uk Tel: 01865 289470
Lead Psychiatrist	Dr Ciaran Mulholland School of Medicine The Queen's University of Belfast Room 02.033 – Whitla Medical Building United Kingdom BT9 7BL Email: c.c.mulholland@qub.ac.uk Tel: +44 (0)2894465211 Mobile: 07703736713
Lead Training compassionate resilience stabilisation	Dr Deborah Lee BerkshireTraumatic Stress & South Central Veteran Mental Health Services Berkshire NHS Foundation Trust Traumatic Stress Service, Erleigh House Whiteknights Campus, University of Reading Reading RG6 6B Email: deborah.lee@berkshire.nhs.uk Tel: 01182143261
Committees	**Trial Steering Committee** **Chair:** Professor Tim Dalgleish: Tim.Dalgleish@mrc-cbu.ac.uk **Member [academic]:** Dr Patrick Smith: patrick.smith@kcl.ac.uk **Service User Rep:** Mr Paul Harte Paul.harte@lockton.com **Statistician:** Dr Mark McCann, Glasgow University mark.mccann@glasgow.ac.uk **Data Management Committee** to be appointed

2. SYNOPSIS

Trial Title	Does a Phased Approach Enhance Outcomes for Trauma-Focused Cognitive Therapy for Complex Posttraumatic Stress Disorder (CT-PTSD)?	
Internal ref. no. (or short title)	Does a phased approach enhance outcomes for CT for Complex PTSD [PHASE- NON PHASED TF-CT CPTSD Trial]	
Trial Design	Randomized controlled trial (stratified; minimisation method)	
Trial Participants	Men and women, 18 years and above, meeting ICD-11 diagnostic criteria for complex posttraumatic stress disorder	
Planned Sample Size	350	
Treatment duration	24 weeks	
Follow up duration	1 year post randomisation	
Planned Trial Period	42 weeks	
	Objectives	**Outcome Measures**
Primary	1: Is phased CT-PTSD superior to non-phased CT-PTSD in improving symptoms of CPTSD?	1a. International Trauma Questionnaire (ITQ) at 26 weeks post randomisation[36] 1b. ITQ[36] and PCL-5[37] at 9, 17, 39 and 52 weeks; International Trauma Interview (ITI)[32] at 26 and 52 weeks
Secondary	2. Does phased CT-PTSD lead to greater improvement in depression, anxiety, disability, well-being, and quality of life than non-phased CT-PTSD?	2. Depression: Patient Health Questionnaire (PHQ-9)[38] Anxiety: Generalized Anxiety Disorder Scale (GAD-7)[39] Disability: Work and Social Adjustment Scale (WSAS)[40] Well-being: WHO(Five) Well-Being Index (WHO-5)[41] at 9, 17, 26, 39 and 52 Weeks; Quality of Life: Endicott Quality of Life (QoL) Scale[42] at 9, 26, 39 and 52 Weeks
	3. Is phased CT-PTSD superior to non-phased CT-PTSD in terms of acceptability and compliance with treatment and treatment satisfaction?	3. Credibility/Expectancy Scale (CES)[54] at 2 and 10 weeks; attendance and adherence to interventions (therapist record); drop-outs from treatment and reasons; Patient Experience

		Questionnaire (PEQ)[43] at 26 weeks.
	4. Is phased CT-PTSD cost-effective compared to non-phased CT-PTSD, i.e. are the costs per patient with a clinical improvement in CPTSD symptoms and costs per quality-adjusted life year (QALY) gained improved with phased CT-PTSD?	4. EuroQoL EQ-5D-5L Instrument[44]; Recovering Quality of Life (ReQoL) Scale[45] Client Service Receipt Inventory (CSRI)[46] Employment status and state benefits Treatment delivery costs (TDCs; based on min of therapy received from therapy record) iMTA Productivity Cost Questionnaire, short form (PCQ)[60]
Tertiary	1. Do changes in PTSD-specific (Trauma-related appraisals, memory characteristics and maintaining cognitive-behavioural strategies) and nonspecific factors (therapeutic alliance, self-efficacy,self-criticism) mediate improvement in CPTSD symptoms? Do baseline levels moderate outcomes? 2. What is the relationship between changes in CPTSD symptoms and sleep?	1. Posttraumatic Cognitions Inventory (PCI)[47], short version Trauma Memory Questionnaire (TMQ)[48], short version Response to Intrusions Questionnaire (RIQ)[49,50], short version Safety Behaviours Questionnaire (SBQ)[20], short version Trait-State Dissociation Questionnaire (TSDQ)[50], short version Forms of Self-Criticising/ Attacking and Self-Reassuring Scale (FSCRS)[51] Compassionate Resilience Scale (CRS) Affect without Recollection Scale (ARS) Working Alliance Inventory (WAI)[52] 2. Insomnia Severity Index (ISI)[53]

Treatment arm(s)	1. Non-phased trauma-focused cognitive therapy for PTSD (non-phased CT-PTSD) 2. Phased trauma-focused cognitive therapy for PTSD (phased CT-PTSD)

3. ABBREVIATIONS

ACE(s)	Adverse Childhood Experience(s)
AE	Adverse event
AEf	Adverse effect of treatment
AR	Adverse reaction
AUDIT	Alcohol Use Disorders Identification Test
CES	(Borkovec and Nau's/B&N's) Credibility/Expectancy Scale
CFT	Compassion-Focussed Therapy
CI	Chief Investigator
CSRI	Client Service Receipt Inventory
CONSORT	Consolidated Standards of Reporting Trials
CPTSD	Complex Posttraumatic Stress Disorder
CR	Compassion(ate) resilience
(e)CRF	(electronic) Clinical Research File/Folder
CR-FAC	Clinical Research Facility
CRN/NICRN	Clinical Research Network/Northern Ireland Clinical Research Network
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CT-PTSD	Cognitive Therapy for Post-Traumatic Stress Disorder
CTI-MD/MP(s)	Clinical Trials of Investigational Medical Device(s)/Medicinal Product(s)
CTRG	Clinical Trials and Research Governance
CTU	(Primary Care (PC-) Clinical Trials Unit
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders 4th Edition/5th Edition
(NI)ECR	(Northern Ireland) Electronic Care Record(s)
EQ-5D-5L	EuroQol five-dimensional five-level questionnaire
FSCRS	The Forms of Self-Criticising/Attacking & Self-Reassuring Scale
GAD-7	Generalized Anxiety Disorder seven-item self-report questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HSC	Health and Social Care [Trust/-B (Board) – Northern Ireland]
IAPT	Improving Access to Psychological Therapies

ICD-11	International Classification of Diseases, 11th Edition
ICERs	Incremental Cost-effectiveness Ratios
ICF	Informed Consent Form
iCT-PTSD	Internet-delivered cognitive therapy [for PTSD]
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISI	Insomnia Severity Index
IRAS	Integrated Research Application System
IRR	Inter-rater Reliability (statistic)
ITI	International Trauma Interview
ITQ/ICD-TQ	International Trauma Questionnaire/ICD-11 Trauma Questionnaire
ITT	Intention-to-Treat
LEC-5	Life Events Checklist for DSM-5
MAR	Missing at Random
MDQ	Mental Defeat Questionnaire
MHRA	Medicines and Healthcare products Regulatory Agency
NHS-E	National Health Service [-England]
NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
NRES	National Research Ethics Service [England]
ORECNI	Office for Research Ethics Committees Northern Ireland
PCL-5	Posttraumatic stress disorder Checklist for DSM-5
PDSQ	Psychiatric Diagnostic Screening Questionnaire
PEQ	Patient Experience Questionnaire
PI	Principal Investigator
PIL/PIS	Participant/Patient Information Leaflet/Sheet
PHQ-9	Patient Health Questionnaire, 9 item version
PPI	Patient and Public Involvement [process/group]
PTCI	Posttraumatic Cognitions Inventory
PTSD	Posttraumatic stress disorder
QALY	Quality-adjusted life year(s)
QOL	Quality of Life (measure)
RCT	Randomised controlled trial
R&D	NHS-E/HSC Trust R&D Department
REC	Research Ethics Committee

ReQoL	Recovering Quality of Life Scale
RIQ	Response to Intrusions Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
(SU)SAR	(Suspected Unexpected) Serious Adverse Reaction
SBQ	Safety Behaviours Questionnaire
SDV	Source Data Verification
SOP(s)	Standard Operating Procedure(s)
TSDQ	Trait-State Dissociation Questionnaire
TAU	Treatment as Usual
TDCs	Treatment Delivery Costs
TF-CBT	Trauma-focused Cognitive Behaviour Therapy
TMF	Trial Master File
TMG/C	Trial Management Group/Committee
TMQ	Trauma Memory Questionnaire
TSC	Trial Steering Committee
TSG	Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group
WAI	Working Alliance Inventory
WHO	World Health Organisation
WSAS	Work and Social Adjustment Scale

4. BACKGROUND AND RATIONALE

Complex posttraumatic stress disorder (CPTSD) is a highly distressing and disabling mental disorder. It is common among people who have experienced very long or repeated severe traumas such as childhood sexual abuse or civil conflict but can also occur after other traumas. The World Health Organisation [WHO] has recently acknowledged CPTSD as a distinct clinical condition in the 11th edition in the *International Classification of Diseases* (ICD-11) [1]. This decision is based on data showing that, in addition to the core symptoms of PTSD, three key areas of dysfunction in self-regulation (i.e. emotional dysregulation, interpersonal difficulties, and negative self-concept) are common in people who have experienced prolonged or repeated trauma (e.g. childhood sexual abuse, civil conflict, torture or combat), can occur after other traumas, and are distinguishable from the core symptoms of PTSD (i.e. reexperiencing, avoidance and hyperarousal). ICD-11 has therefore restricted the diagnosis of PTSD to these three core symptom clusters and thus, defined PTSD more narrowly than previous versions of ICD and the American Psychiatric Association's *Diagnostic and Statistical Manual for Mental Disorders* (e.g. DSM-5) [2]. Research shows that the new diagnosis of CPTSD is common and highly disabling. CPTSD, as defined in ICD-11, is more prevalent than ICD-11 PTSD (point-prevalence 5.2% versus 2.1%) [3] and is also associated with greater impairment in functioning than ICD-11 PTSD [4].

Patients with CPTSD are currently seen in a wide range of treatment services across the UK, and treatment protocols differ between services. Some services offer a phased approach to treatment, while others do not. Trauma-focused psychological treatments recommended by the UK's National Institute of Clinical Excellence (NICE) [5] improve symptoms of PTSD following traumatising experiences [6]. However, it is unclear whether they improve all of the different CPTSD symptoms (for example, evidence is sparse for emotional dysregulation and interpersonal difficulties [7]), whether phased approaches improve outcomes in patients with CPTSD compared to standard trauma-focused psychological treatments recommended by NICE [5], and which patients would benefit most from a phased approach. Answering these questions empirically would help ensure patients with CPTSD receive the most appropriate and effective care for their condition, and thus decrease their distress, improve their social and occupational functioning and decrease costs associated with the provision and seeking of treatment. Better treatments for people with CPTSD would also decrease impact of the disorder on their families. NICE [5] has identified studies of psychological therapies for CPTSD as a priority for research.

Trauma-focused psychological treatments are recommended as first-line treatments for PTSD in NICE [5], and international guidelines. However, much of the evidence base on which these guidelines are based cite use of a DSM diagnosis of PTSD, and it is therefore currently unclear to what extent the findings generalise to CPTSD as defined by ICD-11. Although studies support the validity of the ICD-11 CPTSD concept [8], there is still a lack of consensus in the field about a distinction between severe PTSD and complex PTSD [1, 2]. CPTSD also shares common characteristics with other conditions described in ICD10/-11 and DSM-4/5, including emotionally unstable personality disorder, dissociative disorders, and medically unexplained symptoms.

There is currently a lack of consensus about effective treatment components for CPTSD. While many clinicians and researchers advocate a phased approach to treatment, where the trauma-focused work is preceded by a period of "stabilisation" [9,10], the updated NICE guidelines on PTSD [5], reported that "the evidence base for stabilisation and reintegration/reconnection is limited… and the development of ICD-11 has finally allowed a common understanding of CPTSD which should pave the way for important research." To date, there is limited empirical evidence that phased interventions are more effective or acceptable than standard trauma-focused interventions (62). Several of the NICE-recommended evidenced-based treatment programmes for PTSD do not use a phased approach and have been effective in people with PTSD of varying complexity in RCTs and other effectiveness studies measuring changes in PTSD and comorbid symptoms [e.g., 11-18]. However, a recent meta-analysis [7] concluded that there is limited evidence that standard trauma-focused treatments are effective for the emotional dysregulation and interpersonal problems in CPTSD; so further studies addressing whether outcomes can be improved by psychological therapies are needed.

Trauma-focused cognitive therapy (CT-PTSD) [11-16] is one of the NICE-recommended first-line psychological treatments for PTSD. It uses an individualised formulation of the patient's problems that allows a flexible order of delivery of treatment components. This treatment is based on Ehlers and Clark's [19] cognitive model of PTSD, which has received empirical support [20-25]. This model suggests that people with PTSD (including those that would meet ICD-11 criteria for CPTSD) perceive a serious internal or external current threat that has two sources: (i) excessively negative appraisals (or personal meanings e.g., "I am inadequate", "I cannot trust other people) of the trauma and/or its sequelae, and; (ii) characteristics of trauma memories that lead to re-experiencing symptoms. The problem is maintained by cognitive strategies and behaviours (such as thought suppression, rumination, safety-seeking behaviours) that are intended to reduce the sense of current threat but maintain the problem by preventing change in the appraisals and trauma memory, and/or lead to increases in symptoms. Non-phased CT-PTSD addresses these maintaining factors by identifying and changing unhelpful appraisals, elaborating trauma memories and discriminating triggers, and helping patients drop unhelpful coping strategies.

There are theoretical and empirical reasons to hypothesise that non-phased CT-PTSD is effective for the CPTSD symptoms of emotional dysregulation, interpersonal difficulties, and negative self-concept: (a) the treatment focuses on reducing re-experiencing symptoms, including affective reactions that the patient does not recognise as trauma responses; (b) trauma-focused work and *reclaiming your life* assignments reduce irritability and social withdrawal, and; (c) work on appraisals focuses on negative appraisals of the self. In line with this hypothesis, non-phased CT-PTSD has been found to be acceptable and effective in RCTs and effectiveness studies that included patients that would meet ICD-11 CPTSD criteria, with large effects for both PTSD symptoms, social and occupational disability, and quality of life (QoL) measures [11,13-16]. However, these studies used DSM criteria for PTSD and did not assess the full range of symptoms now included the ICD-11 diagnosis of CPTSD such that the effects of non-phased CT-PTSD on the full range of CPTSD symptoms require further investigation.

Furthermore, for patients with CPTSD, a phased approach with preparatory work on managing emotions and interpersonal problems may allow patients to engage more productively with the trauma-focused work, especially if the traumas occurred in childhood or if the patient experiences strong shame and self-loathing. *Compassion Resilience* (based on [26]) offers a promising therapeutic contribution as part of a phased approach [9, 10], as it targets the three areas of poor self-regulation defined in ICD-11 [27].

Work by Lee and colleagues showed that a compassion-focused group treatment conducted prior to trauma-focused cognitive behavioural treatment (TF-CBT) led to large changes in CPTSD symptoms [28-30], and 72% of patients recovered with the phased treatment. *Compassion Resilience* is also part of a phased treatment that was recently shown to be superior to cognitive processing therapy [31], a trauma-focused cognitive treatment that differs from CT-PTSD in that is does not include detailed work on trauma memories and memory triggers. Thus, it remains to be tested whether a compassion-focused stabilisation phase enhances outcomes for patients with CPTSD who are subsequently treated with CT-PTSD.

The study will compare the delivery of CT-PTSD with and without a phased element. In one group, the treatment involves the immediate provision of the CT-PTSD protocol, which is adapted individually to each patient, and in the other group CT-PTSD is provided after 8 sessions of compassionate resilience training (phased CT-PTSD). The study will consider whether both approaches work equally well or whether there are advantages in providing a phased approach, or a non-phased approach for some groups of patients. In the phased arm, treatment commences with a compassion-focused stabilisation phase that aims to build compassionate resilience in order to enhance emotion regulation and management of interpersonal difficulties and to improve risk management. We aim to address the following questions:

1. Is phased CT-PTSD superior to non-phased CT-PTSD in terms of acceptability, compliance and satisfaction with treatment?
2. Is phased CT-PTSD superior to non-phased CT-PTSD in improving symptoms of CPTSD, comorbid depression, well-being, disability, and quality of life?
3. Is phased CT-PTSD cost-efficient compared to non-phased CT-PTSD in terms of cost per participants with a clinical improvement in PTSD symptoms and costs per quality-adjusted life year (QALY) gained?

We will also explore whether there are subgroups of patients with CPTSD for whom the advantages of a phased approach are greater than for others. For example, differences between phased and non-phased CT-PTSD may be especially pronounced for CPTSD following childhood sexual abuse, or for participants who self-harm.

5. OVERVIEW OF OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of planned evaluation of this outcome measure
Primary Objective 1. Is phased CT-PTSD superior to non-phased CT-PTSD for Complex PTSD, i.e. does it lead to greater improvement in Complex PTSD symptoms?	1a. Complex PTSD symptom severity, as assessed by the International Trauma Questionnaire (ITQ)[36] 1b. Secondary measures of complex PTSD symptom severity, as assessed by the International Trauma Questionnaire (ITQ)[36] at other assessment points; by independent interviewers (International Trauma Interview, ITI)[32] and PTSD Symptom Checklist, (PCL-5))[37]	1a. ITQ at 26 weeks post randomisation[36] 1b. ITQ at 9, 17, 39 and 52 weeks; ITI[32] at 26 and 52 weeks and PCL-5[37] at 9, 17, 39 and 52 weeks
Secondary Objectives (see 1. above) 2. Does phased CT-PTSD lead to greater improvement in depression, disability, well-being, and quality of life than non-phased CT-PTSD?	2. Depression: Patient Health Questionnaire (PHQ-9)[38] Anxiety: Generalized Anxiety Disorder 7-item (GAD-7)[39] Disability: Work and Social Adjustment Scale (WSAS)[40] Well-being: WHO (Five) Well-Being Index[41] Quality of Life: Endicott Quality of Life (QoL) Scale[42]	2. PHQ-9, GAD-7, WSAS, WHO Well-Being Index at 9, 17, 26, 39, 52 weeks; QOL Scale at 9, 26, 39 and 52 weeks
3. Is phased CT-PTSD superior to non-phased CT-PTSD in terms of acceptability and compliance with treatment and treatment satisfaction?	3a. Borkovec and Nau's Credibility/Expectancy (CES) Scale[54] 3b. attendance and adherence to interventions (therapist report) 3c. drop-outs from treatment and reasons. 3d. IAPT Patient Experience Questionnaire (PEQ)[43]	3a. 2 and 10 weeks 3b-d. 26 weeks
Tertiary Objectives 1. Do changes in PTSD-specific processes (Trauma-related appraisals, memory	1a. PTCI[47], short version 1b. Trauma Memory Questionnaire (TMQ)[48], short version.	1. Scores on mediator measures a. to f. measured at baseline

characteristics and maintaining cognitive-behavioural strategies), self-criticism and working alliance mediate improvement in PTSD symptoms with CT-PTSD and phased CT-PTSD?	1c. Response to Intrusions Questionnaire (RIQ)[49,50], short version 1d. Safety Behaviours Questionnaire (SBQ)[20], short version 1e. Trait-State Dissociation Questionnaire (TSDQ)[50], short version 1f. Forms of Self-criticising/Attacking and Self-Reassuring Scale (FSCRS)[51]	and at least monthly during 26 weeks of treatment and ITQ (measured weekly) during 26 weeks of treatment
	1g. Compassionate Resilience Scale (CRS) 1h. Affect without Recollection Scale	1g./1h. Baseline, 9 and 26 weeks
	1i. Working Alliance Inventory (WAI), completed by patients and therapists[52]	1i. weeks 2 and 10
2. Do baseline scores on these measures, demographic or trauma characteristics, comorbidity or treatment credibility moderate differential treatment outcomes?	2a. Baseline measures 1a to 1h; patient registration form; clincial and eligibility assessment, Mental defeat questionnaire	2a. Baseline
	2b. Credibility/Expectancy Scale	2b. 2 weeks and 10 weeks
3.What is the relationship between changes in CPTSD symptoms and sleep?	3. Insomnia Severity Index (ISI)[53]	3. 26 weeks and 52 weeks
4. Is phased CT-PTSD more cost-effective than non-phased CT-PTSD, i.e. do the costs per patient with a clinical improvement in PTSD symptoms and costs per QALY gained improve with the use of phased CT-PTSD?	4a. EuroQol EQ-5D-5L[44] 4b. Recovering Quality of Life (ReQoL) Scale[45] 4c. Client Service Receipt Inventory (CSRI)[46] 4d. Employment status and state benefits 4e. Treatment delivery costs 4f. iMTA Productivity Cost Questionnaire, short form (PCQ)	4. a-d and f. 26 and 52 weeks 4e. 26 weeks (and 39 weeks if additional sessions)
5.How do patients, their families and therapists describe their experience with non-phased and phased CT-PTSD?	5a. Qualitative interviews with patients, family members and therapists 5b. Patients: Patient Experience Questionnaire (PEQ)	5b.Following treatment (after 26 weeks)

6. TRIAL DESIGN

A multicentre, pragmatic, individual randomised, parallel group randomised controlled trial (RCT) comparing the effectiveness of phased CT-PTSD versus non-phased CT-PTSD for adult patients with CPTSD. Embedded in the study will be (a) a treatment process evaluation investigating recruitment rates, drop-outs and compliance, candidate treatment mechanisms, and patient, therapist and service factors that may influence outcome, (b) a qualitative study of patient, family and therapist experience. We will incorporate an internal pilot over the first 6 months of recruitment with pre-specified "go/no-go" criteria.

Blind assessors of treatment outcome will be psychologists trained in the *International Trauma Interview* (ITI) [32] (see section 8.5 for details) who will interview participants at baseline, end of treatment (26 weeks), and at 52 weeks.

Therapists delivering the treatments, the trial administrators and participants will not be blind to treatment randomisation.

7. PARTICIPANT IDENTIFICATION

7.1. Recruiting Research Sites

Patients with CPTSD following a wide range of traumas and severity of CPTSD, are currently seen across a wide range of adult mental health services in Northern Ireland and England (Improving Access to Psychological Therapies (IAPT), secondary care, Specialist Psychological Treatment/ Trauma Services). The participating research sites see patients with a wide range of trauma types, ethnicity and severity of CPTSD and were chosen to maximise the generalizability of the findings and enable the investigation of patient (e.g., trauma type), therapist (e.g., experience with CPTSD) and service factors (e.g. primary, secondary or tertiary care) that may influence outcomes.

Participants will be recruited from: (i) five sites that are part of the Northern Ireland Trauma Network, where a team is located in each of the Health and Social Care Trusts (HSCT) covering rural and urban areas (i.e. Belfast HSCT; Northern HSCT; Southern HSCT; South Eastern HSCT; and Western HSCT), and; (ii) five sites across England covering rural, urban and metropolitan areas (i.e. Berkshire Healthcare NHS Foundation Trust; Camden and Islington NHS Foundation Trust; Oxford Health NHS Foundation Trust; South West London & St. George's NHS Trust; Hertfordshire Partnership University NHS Trust). These sites will provide a good representation of socioeconomic and ethnic diversity of the study population. In England, we will recruit from both Improving Access to Psychological Therapies (IAPT) services and secondary care/specialist Trauma Services to ensure that patients with a wide range of traumas and severity of CPTSD are represented. Northern Ireland has been exposed to a long period of civil conflict and has higher 12-month and life-time prevalence rates of PTSD compared to other countries affected by conflict, including South Africa, Israel / Lebanon [33].

We anticipate, between 2 and 8 trial therapists per site who will identify patients referred to their services that may be eligible for the trial. Each of the sites sees more than 100 patients with CPTSD per year, so that a recruitment target of 35 patients randomised to a treatment arm over 18 months per site appears realistic and achievable. In Northern Ireland, the new Regional Trauma teams offer a specialist service to secondary care mental health teams for PTSD.

Persons with lived experience of CPTSD will be included in all stages of the research, including study design, selection of assessments and development of study protocol standard operating procedures (SOPs) through a patient and public involvement (PPI) process.

7.2 Trial Participants

Participants will be adults (male, female, non-binary) with complex posttraumatic stress disorder (ICD-11 CPTSD) resulting from one or more traumatic events. For interview purposes, secondary diagnoses will be determined at intake to the study using the Psychiatric Diagnostic Screener Questionnaire [PDSQ] [59].

7.2.1 Inclusion Criteria

Inclusion Criteria

1. Aged 18 and above;
2. Willing and able to provide informed consent;
3. Meets ICD-11 diagnostic criteria for CPTSD as determined by the ITI [35];
4. CPTSD is the main psychological problem needing treatment;
5. Willing to be randomised to a treatment arm;
6. If taking psychotropic medication, the dose must be stable for at least 1 month before randomisation to a treatment arm;
7. If currently receiving psychological therapy for CPTSD, this treatment must have ended before randomised to a treatment arm.

7.2.2. Exclusion Criteria

1. History of psychosis;
2. Current substance dependence;
3. Acute serious suicide risk*.

We will aim to recruit a diverse sample building on our experience in the Centre of Evidence and Innovation & School of Social Science, Education and Social Work (SSESW) at Queens University Belfast and Oxford Health NIHR Biomedical Research Centre of raising awareness and encouraging participation in research studies through outreach and public

engagement activities involving local community leaders. We will assist participants who need help with completing questionnaires, and will translate therapy materials and questionnaires into different languages if patients require an interpreter.

We will not exclude individuals who have already had a course of trauma-focused treatment as most people with CPTSD will have had a range of previous treatments, and the quality of delivery and degree of trauma-focus in the treatments delivered is very variable in clinical practice. Our previous work shows that treatment history does not predict outcomes for CT-PTSD [14]. The research team will record participants' treatment history as part of the eligibility assessment.
.* see 8.2 for risk assessments

8. TRIAL PROCEDURES

8.1 Recruitment

After their initial clinical assessments at the respective sites, therapists will explain the possibility of joining the trial to patients that appear potentially suitable. If they are interested and agree to be contacted by the research team, they will receive further information about the trial on the telephone or via videoconferencing from research staff. Research staff will also send interested parties the *Patient Information Sheet* (PIS) and will allow potential participants the opportunity to ask questions. The REC-approved PIS will provide participants with information about: the aims of the study; the eligibility assessment and the participant randomisation procedure; treatment and assessment schedule, details of time and sequence of events involved (including a patient journey flowchart); potential benefits and risks of taking part; ethical approval; sponsor and funder information; data management and confidentiality; the freedom to discontinue at any time; financial reimbursement; and contact details for the research team. Participants will be given at least 24 hours to decide whether they are interested in participating in the trial, and can take as much time as they need.

If they are interested, the research team will invite potential participants to consent for an eligibility assessment (*Informed Consent Form* (ICF – Part 1)) with the baseline questionnaires and the ITI [32] to ascertain that they meet ICD-11 criteria for CPTSD and other inclusion criteria. The independent assessors can conduct this interview via videoconferencing or telephone depending on participant preferences. If the eligibility assessment shows that a potential participant is eligible for the trial, the research team will inform them of the opportunity to ask further questions and if they agree to participate, will request that they sign the REC-approved *Informed Consent Form* (ICF – Part 1) for the trial. Those potential participants who are not eligible, or do not agree, to participate in the trial will be offered treatment as usual (TAU) by the respective service.

8.2 Eligibility Assessment

The participating clinical services will conduct their routine clinical assessment including a risk assessment to identify patients who are potentially suitable for the trial. The research team will conduct the additional elements of the eligibility assessment. Besides the ITI [32], the eligibility assessment includes completing a *Demographics and Medication Use Questionnaire*, the *Life Event Checklist for DSM-5* (LEC-5) [34], The *Adverse Childhood Experiences Questionnaire*, 11-item version (ACE-Q) [61], *Mental Defeat Questionnaire* (MDQ) [20] and the *Alcohol Use Disorders Identification Test* (AUDIT) [35].

8.3 Informed Consent

A member of the research team will obtain Written Informed Consent in two steps using the ICF (consent to eligibility assessment – Part 1, and consent to participation in the trial – Part 2) by means of a participant-dated signature (obtained electronically). Participants will receive detailed written (i.e. the PIS) and verbal information about the exact nature of the assessment and RCT, and what participation will involve for them.

First, as potential participants will initially attend an eligibility assessment to determine whether they have CPTSD and are eligible for the trial, they will give written consent for this assessment (Part 1 of ICF), completed online through a secure electronic database developed by the Clinical Trials Unit (CTU).

If the eligibility assessment confirms that the participant is eligible, and if they agree to participate in the trial, the participant will sign and date the latest approved version of Part 2 of the ICF online through a secure electronic database developed by the CTU, before any trial-specific procedures (e.g., randomisation to a treatment arm, treatment) are performed by the research team. If the participant is not eligible or does not consent to participate in the trial, they will receive TAU at the participating service or referred to another service, if more appropriate, and will not be randomised to a treatment arm in the trial. If the participant would like more time to think about participation, has not been on a stable dose of medication for 1 month, and/or is currently receiving another psychological treatment for PTSD, Part 2 of the ICF can be completed at the end of the respective period when the individual becomes eligible.

The participant will be given as much time as they wish (at least 24 hours) to consider the information about the trial, and will have the opportunity to question the trial team, their GP or other independent parties to decide whether they will participate in the trial.

The person who obtains the written consent for each part of the process must be suitably qualified and experienced, and have been authorised to do so by one of the CIs, or their delegate (e.g. a Principal Investigator (PI)/local collaborator (LC)) at a site, in collaboration with her/his respective NHS-E/HSC R&D/Research Office). A designated staff member from the trial team will email copies of the signed ICF (Part 1 and then, Part 2) to the participant and the trial site. The CTU will retain the original electronically signed ICF (Part 1 and 2).

The research team will invite and consent a small group of partners or family members to participate in an interview to discuss their experience, impressions and observations of their partner/ family member going through treatment. They will be given the Partners and Family Members Information Sheet and Consent Form.

Therapists participating in the trial will be nominated by their service and given the Clinician Information Sheet and Consent Forms informing them about the training and supervision requirements and information to be provided for the trial (basic demographics and previous experience, record of therapy sessions, recordings of sessions. Working Alliance Scale, and for a subgroup qualitative interview about experience with treatment delivery).

Records of consent will be held at the respective national research centres, Queens University Belfast and University of Oxford.

8.4 Group Allocation

After the eligibility assessment and consenting procedure (ICF Part 1), a member of the research team will will randomise eligible participants to one of the two treatment arms (phased CT-PTSD, non-phased CT-PTSD) using a 1:1 ratio, using a fully validated web-based clinical trial randomisation system, *Sortition*, with a non-deterministic minimisation algorithm. The use of *Sortition* will ensure that the variables site, age at main trauma (<18 vs 18 and above), whether an interpreter is needed (yes vs no), severity of PTSD symptoms on the main outcome measure, the *International Trauma Questionnaire* (ITQ) [36] score assessing ICD-11 CPTSD symptom severity (high versus low), all recorded as part of the eligibility assessment, are stratified across participants. The randomisation sequence is not visible to the research staff who generate the treatment randomisation with the programme to ensure treatment concealment. For participants taking psychotropic medication, group randomisation will take place after they have been on a stable dose for 1 month. The research centre(s) will inform delegated personnel at the trial site(s) by email of participants' randomisation outcome following the *Sortition* process to allow treatment to commence. Therapists and the research team will record participant's journey through the study at the study sites. Key data concerning consents, withdrawals and outcomes at sites will be uploaded to NHS/HSC systems for research recording and auditing purposes.

8.5 Blinding

The independent assessors, who will interview participants to obtain observer assessments of treatment outcome with the *International Trauma Interview* (ITI) [32], will be blind to participants' treatment variables. They will receive comprehensive training in conducting and scoring the interview. Inter-rater reliability (IRR) will be determined during the pilot phase of the study, and discrepancies will be resolved by consensus. The trial statistician who

performs the statistical analysis will also be blind to treatment allocation, therapist and trial site.

Therapists delivering the treatments, research operations staff and participants themselves will not be blind to treatment allocation due to the nature of the intervention.

8.6 Trial Assessments

8.6.1 Primary outcome and assessment endpoint

The primary assessment endpoint is 26 weeks post randomisation process (i.e., end of treatment after the planned 24 treatment sessions). The primary outcome measure is severity of CPTSD symptoms as measured by the ITQ [36].

The ITQ is a validated self-report measure of complex PTSD symptoms according to ICD-11[1]. This questionnaire will be given at all 7 assessment points (see **Appendix B**) and is expected to yield the most complete data. This questionnaire has 12 items that are scored from 0 to 4. There are two items for each of the 6 symptom clusters of CPTSD defined in ICD-11 [1]. The first three (namely re-experiencing, avoidance, hypervigilance/startle) define PTSD. Problems in self-organisation required to diagnose CPTSD in addition to the PTSD symptoms are emotion dysregulation, negative self-concept, and disturbances in relationships. A sum score (ranging from 0 to 48) is calculated to indicate the severity of CPTSD symptoms. Functional impairment using this instrument is also scored for clinical interpretation and analysis purposes. The questionnaire will also be given weekly throughout treatment to help therapists with treatment decisions.

8.6.2 Secondary Outcomes

Secondary outcome measures include the ITI, the validated rater-administered measure of complex PTSD symptoms according to ICD-11 [32], which will be obtained at the eligibility assessment, and the 26 and 52 week assessments. A trained independent assessor blind to the participant's treatment arm will conduct this assessment.

Further measures of symptom severity and interference with functioning for each patient will be given at the main assessment points, including the standard outcome measures administered routinely at every therapy session in the participating NHS-E/HSC services i.e. the *PTSD Checklist for DSM-5* (PCL-5) [37], the *Patient Health Questionnaire* (PHQ-9) [38], to assess symptoms of depression; and the *Generalized Anxiety Disorder Scale, 7-items version* (GAD-7) [39] to assess symptoms of anxiety; the *Work and Social Adjustment Scale* (WSAS) [40] to assess disability and interference with functioning. In addition, patients will complete the brief 5-item *WHO(Five) Well-Being Index* [41] to assess psychological wellbeing and the *Endicott Quality of Life* (QoL) *Scale* [42] to assess different areas of quality of life.

At 26 weeks, the IAPT *Patient Experience Questionnaire* (PEQ) [43], will provide qualitative and quantitative information on patients' treatment experience.

Participants will also complete **health economic measures,** including: health-related quality of life (measured by the EQ5D-5L questionnaire [44] and the *Recovering Quality of Life* (ReQoL) *Scale* [45]) and use of health and social care services, productivity loss and informal care due to PTSD (measured by an adapted version of the *Client Service Receipt Inventory* (CSRI) [46]) and *iMTA Productivity Cost Questionnaire* [60] at baseline, 26, and 52 weeks.

8.6.3 Tertiary Outcomes

Process measures include short questionnaires of processes that maintain PTSD and change with treatment (appraisals, memory characteristics and unhelpful coping) and the working alliance between therapist and patient: *Posttraumatic Cognitions Inventory* (PTCI) [47], *Trauma Memory Questionnaire* (TMQ) [48], *Responses to Intrusions Questionnaire* (RIQ) [49], *Safety Behaviours Questionnaire* (SBQ) [20], *Trait-State Dissociation Questionnaire* (TSDQ) [50], *Forms of Self-Criticising/Attacking and Self-Reassuring Scale* (FSCRS) [51], *Compassionate Resilience Scale* (CRS) and *Working Alliance Inventory* (WAI) [52]. Sleep disturbance will be assessed with the *Insomnia Severity Index* (ISI) [53].

Treatment credibility will be assessed with the short self-report Borkovec and Nau's *Credibility/Expectancy Scale* (CES) [54] in weeks 2 and 10 of treatment.

Appendix B gives an overview of the measures given at the assessment visits and Appendix E lists all live (and retired) study measures.

8.6.4 Assessment Points and Procedures

As shown in the patient flowchart (**Appendix A**), the research team will obtain measures on up to 7 occasions:

- Enrolment [+ Baseline/Visit 1 if deemed eligible for the trial]
- 9 weeks after treatment arm randomisation (post the 8-session phase 1 of phased CT-PTSD)
- 17 weeks after treatment arm randomisation
- 26 weeks after treatment arm randomisation (post the planned end of treatment),
- 39 weeks after treatment arm randomisation (Follow-up 1, 3 months after planned end of treatment),

- 52 weeks after treatment arm randomisation (Follow-up 2, 6 months after planned end of treatment),

Assessments at baseline/Visit 1, 26 and 52 weeks will include both self-report questionnaires and a standardised structured interview (ITI [32]) conducted by an independent assessor who is blinded to treatment arm (estimated total patient time 1.5 to 2 hours). These assessments will take place by phone or video call, if the participant prefers. The other three assessments will be self-report questionnaires only (estimated total patient time 30 - 45 min).
Questionnaires at baseline/Visit 1, and subsequent assessments at 9, 17, 26, 39 and 52 weeks, will be collected online via secure (https) networks and stored in a secure encrypted electronic database (REDCap) developed by the CTU.
Invitations to, and reminders for, the ITI [32] assessments and questionnaire measures will be sent out by the trial administrators and CTU staff.

8.6.5 Monitoring for potential negative effects of therapy

We will also report the percentage of patients who experience symptom deterioration, i.e., feel worse rather than better after therapy, i.e. a statistically reliable change in an unfavourable direction on the ITQ [36] or ITI [32], judged for clinical significance.

8.7 Summary of Assessment Interviews, Questionnaires and Rating Forms

Eligibility Assessments:
- Clinical assessment incl. risk assessment, demographic and medication use
- Psychiatric Diagnostic Screener Questionnaire [PDSQ] [59].
- International Trauma Interview (ITI) [32] and International Trauma Questionnaire (ITQ) [36])
- Life Event Checklist (LEC-5) [34] and Mental Defeat Questionnaire (MDQ) [20]
- The Adverse Childhood Experiences Questionnaire, 11-item version (ACE-Q) [61]
- Alcohol Use Disorders Identification Test (AUDIT) [35])

PTSD Measures
- ITQ) [36] and ITI, [32], see above)
- PTSD Checklist for DSM 5 (PCL-5) [37]

Other Symptom/Well-Being Measures
- Patient Health Questionnaire (PHQ-9) [38]
- Generalised Anxiety Disorder Scale (GAD-7) [39]
- Work and Social Adjustment Scale (WSAS) [40]
- WHO (Five) Well-Being Index [41]
- Endicott Quality of Life (QoL) [42]

Patient Satisfaction
- IAPT Patient Experience Questionnaire (PEQ) [43]

Health Economics Measures (see 11.1.3)

- EuroQoL EQ-5D-5L [44]
- Recovering Quality of Life (ReQoL) Scale [45]
- Client Service Receipt Inventory (CSRI) [46]
- iMTA productivity cost questionnaire [60]
- Treatment Delivery Costs

Process Measures (see 11.1.2)

- Posttraumatic Cognitions Inventory (PTCI), short version [47]
- Trauma Memory Questionnaire (TMQ), short version [48]
- Response to Intrusions Questionnaire (RIQ), short version [49]
- Safety Behaviours Questionnaire (SBQ), short version [20]
- Trait-State Dissociation Questionnaire (TSDQ), short version [50]
- Forms of Self-Criticising/Attacking and Self-Assuring Scale (FSCRS) [51]
- Compassionate Resilience Scale (CRS)
- Working Alliance Inventory (WAI) [52]
- Insomnia Severity Index (ISI) [53]

Treatment Credibility Measure (see 9.3)

- Credibility Rating (patient) – CES [54]

8.8. Discontinuation/Withdrawal of Participants from Trial Treatment and Loss to Follow-up

Dropout, or premature termination from the study or treatment at any point after the randomisation procedure will be recorded along with reason for discontinuation or termination. This includes termination in the event of an SAE or AR (see 10).

8.8.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. If a participant considers withdrawing from the trial, they will be given the opportunity to discuss this decision with trial staff, who will answer any queries and clarify their options (including provision of the minimum dataset, as defined here, in section 8.8.1 of the protocol). The participants' care will not be affected at any time by declining to participate or withdrawing from the trial. If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal from the treatment intervention
2. Withdrawal from follow-up interviews/questionnaires
3. Withdrawal from the treatment intervention and also the follow-up interviews/questionnaires.

In circumstances 1-3, the withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. Data concerning first contacts, study participation, and any withdrawal of participation will be retained for all potentially eligible and selected participants, as well as participants who have withdrawn, for research auditing purposes.

A participant may be withdrawn by the research team from the intervention for the following reasons:

- Any alteration in the participant's condition that justifies the discontinuation of the intervention in the Investigators' opinion. For example, developing a condition that would exclude them from the study based on the eligibility criteria or a change in their clinical condition requiring urgent other treatment (e.g. the patient has developed a psychotic disorder, a SAE/SUSAR).

Participants who withdraw/are withdrawn from the intervention part of the trial only will continue in follow up unless they withdraw their consent for this.

Withdrawn patients will not be replaced.

8.8.2 Loss to follow up

Unless a participant has withdrawn consent to participation, repeated attempts (up to 5) using different approaches will be made to contact participants who cannot be easily contacted. In a step-wise manner, this will involve checking contact details with their study therapist, or study therapists' records at the trial site, calling the individual on all contact numbers provided on various days of the week and at different times, sending e-mails and a letter to the addresses provided. If the research centre staff still cannot make contact with the participant, the individual's GP will be contacted to check contact details are correct and up-to-date (GP information will be accessible through therapist's records, medical notes and/or [NI]ECR at the research site) and the mechanisms for obtaining participant contact details already noted in section 8.8.2). If these attempts do not result in contact being made within one month of loss of contact or the planned follow-up, trial staff at the research centre(s) will send a letter asking the participant to re-establish contact, if they are able to, and advising that they will be contacted again at the next follow-up point, unless they advise otherwise or indicate that they no longer wish to participate in the trial. For any participant reluctant to complete the full outcome assessment at follow-up, we will attempt to gain the ITQ, PHQ-9 and WSAS as a minimum dataset.
As much information as possible will be collected from participants who are protocol non-adherers, with a minimum of the primary and secondary outcome measures and reasons for non-adherence recorded for all participants randomised to a treatment arm.

8.9. Definition of End of Trial and End of Study

The end of trial is the date of the last follow up with the last participant. The end of study is the date of close-out and completion of all study-related activities, as shown in Appendix C.

9. INTERVENTIONS

The RCT will compare two treatment arms:

9.1. Non-phased CT-PTSD

Non-phased CT-PTSD will follow the Ehlers et al. CT-PTSD manual [55] and will be delivered over/up to 24 sessions. Sessions will be up to 90 min for trauma-focused sessions. Core interventions are as follows:

- The therapist and client collaboratively develop an *individualized case formulation,* i.e., an individualized version of Ehlers and Clark's [20] model of PTSD, which serves as the framework for therapy. Treatment procedures are tailored to the formulation.
- *Reclaiming/rebuilding your life assignments* are designed from the first session onward to address the patient's perceived permanent change after trauma and involve reclaiming or rebuilding activities and social contacts.
- *Changing problematic appraisals* of the traumas and their sequelae (e.g., responses of others, physical consequences, losses, symptoms of PTSD) involves information, guided discovery, and *behavioural experiments* throughout treatment. For appraisals of the traumas, this is closely integrated with the *updating memories procedure*.
- *Updating trauma memories* is a three-step procedure that includes: (1) accessing memories of the worst moments during the traumatic events and their currently threatening meanings; (2) identifying information that updates these meanings (either information from the course of events during the trauma or from guided discovery and testing of predictions), and; (3) linking the new meanings to the worst moments in memory.
- *Discrimination training with triggers of reexperiencing* involves systematically spotting idiosyncratic triggers (often subtle sensory cues) and learning to discriminate between "now" (cues in a new safe context) and "then" (cues in the traumatic event).
- A *site visit* completes the memory updating and trigger discrimination (in person or virtual).
- *Dropping unhelpful behaviours and cognitive processes* commonly includes discussing their advantages and disadvantages and *behavioural experiments,* whereby the patient experiments with reducing unhelpful strategies such as rumination, hypervigilance for threat, thought suppression, and excessive precautions (safety behaviours).
- A *blueprint* summarizes what the client has learned in treatment and includes plans for any setbacks.

Some participants recruited from specialist trauma services will need to be offered up to 8 extra sessions to complete treatment if they have not completed work on all their traumas after 24 sessions (this is in line with NHS-E specialised commissioning of 32 session model for

complex PTSD in Veteran communities). The total number of sessions will be recorded for analysis purposes.

9.2. Phased CT-PTSD

Phased CT-PTSD will comprise 2 phases. In phase 1, participants will receive 8 sessions of compassion-focused stabilisation, adapted from Lee's protocol [28]. If indicated, this can be supplemented by other stabilisation techniques appropriate for a patient.
Compassion Resilience targets the development of a compassionate mind in order to:

- Improve affect regulation, interpersonal functioning,
- Increase self- compassion, psychological flexibility, and distress tolerance, and
- Reduce shame and self-loathing.

The intervention [28] is a hybrid of psychoeducation and training exercises to enhance skills development before engagement in trauma-focused memory work. Treatment components include: psychoeducation, training in mindful attention, soothing rhythm training, compassionate imagery, emotion differentiation, safe place imagery, compassionate dialogue, psychological flexibility, mental rehearsal, and compassion-focused problem solving.

In phase 2, participants will receive 16 sessions of CT-PTSD (the planned end of treatment is after 24 sessions). As previously noted, some participants in specialist services will be offered up to 8 extra sessions if required.

9.3 Therapists, Treatment Fidelity and Credibility

Therapists will be clinical psychologists or CBT therapists with at least basic training in CT-PTSD identified by the participating services. They will attend workshops on treating CPTSD with CT-PTSD, Compassion Resilience and stabilisation for the phased treatment.
Therapists will receive monthly group supervision to ensure adherence to the protocol and quality of treatment delivery. Supervisors will be Dr Michael Duffy, Mr Paul Quinn, Mr Brendan Armstrong, Dr Kevin Dyer, Dr Deborah Lee, Dr Nick Grey, Dr Hannah Murray, Dr Richard Stott and Dr Martha Nicholson.

Treatment fidelity (i.e. treatment adherence and therapist competence) will be assessed by trained psychologists (i.e. treatment fidelity raters) who are not delivering the trial treatments and are different from the independent assessors conducting the ISI sessions. Randomly selected audio or video recordings of the therapy sessions between therapist and patient will be scored for: (1) adherence to treatment components, and (2) competence using suitable items from the *Cognitive Therapy Rating Scale* [56]. Participants are made aware of this in the PIS. Raters will not have access to patients' personal information other than the type of traumas addressed in treatment. They will have no contact with the participants.

The 3-item self-report Borkovec and Nau's *Credibility/Expectancy Scale* (CES) [34] taken in weeks 2 and 10 of treatment will assess how credible patients find the treatment (week 10 is the second session of trauma-focused work in the phased CT-PTSD condition).

10. SAFETY REPORTING

10.1 Definitions

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

***Note:** The term 'life-threatening' in the definition of 'serious' refers to an event in which the trial participant is at risk of death at the time of the event or it is suspected that use,or continued use, of the intervention would result in the participant's death; it does not refer to an event which, hypothetically, might have caused death if it were more severe. ***Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Adverse effects will be monitored throughout treatment (information provided by the therapist and from independent assessments) and follow-up (information from independent assessments). Any AEs or SAEs will be recorded and evaluated by the Chief Investigators using a standard reporting template (CIs; or another appropriately qualified delegated clinical psychologist from the trial team) for relationship to the treatment and expectedness. The only expected side effect of either intervention that may occur in some instances is a temporary increase in distress as a result of remembering the trauma and encountering trauma reminders. This is mentioned in the information sheet and discussed in therapy sessions before commencing trauma-focused interventions.

10.2 Reporting Procedures for Serious Adverse Events

PIs at each site will be responsible for reporting Serious Adverse Events (SAE) to the CIs, who will then report to the sponsor. A serious adverse event (SAE) occurring to a participant (any time between consent and the final follow-up assessment of the trial) will be reported to the REC that gave a favourable opinion of the study where, in the opinion of the CIs, the event was 'related' (resulted from administration of any of the research procedures) and

'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the CIs becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

10.3 SAE Reporting/Risk of Harm

In addition to the SAE reporting requirements above, for the purposes of this trial, severe self-harm and harm to others will be reported to the CIs (who are responsible for interacting with any personnel assigned to oversee data and safety monitoring within their respective academic institutions, and to maintain submit reports in accordance with organisational policies). Therapists will notify the CIs within 24 hours should they be concerned at any time that a participant has, or is likely to cause significant harm to themselves for the duration of the trial. The therapist will also inform their service manager and the participant's GP. Therapists will inform the appropriate authorities directly should they become concerned at any time that a participant has caused, or is likely to cause, significant harm to others. This information will be recorded in the participant's medical notes (and/or Electronic Care Record(s)). The inclusion/exclusion criteria and withdrawal section of this protocol will assist the determination regarding whether the participant needs to be withdrawn from further participation (see 8.6).

In the event that interviews with participants and/or family members result in disclosure of information related to therapist conduct, this will be brought (by the interviewer/ researcher) to the attention of the CI's who, where necessary, will liaise with the relevant Trust/s.

11. STATISTICS

11.1.4 Embedded Qualitative Study

Interviews with patients, family members and therapists (a total of 40 interviews sampled to represent a range of trauma types and services) will be used to assess experience with phased and non-phased CT-PTSD. Topic areas will be developed with our PPI panels of people with lived experience in England and Northern Ireland. Possible topics informed by existing grounded theory include: disabling symptoms and their change with treatment; obstacles to engaging with treatment; effects on family life and ability to work; experience with the interventions; interventions experienced as more or less helpful; how memory work was tolerated, and; how sense of self changed with treatment. The interviews will be semi-structured (using open and closed questions) and analysed using a Thematic Analysis, both informed by embedded dynamic and emergent PPI and supervisory data-gathering processes.

11.1. Description of Statistical Methods

11.1.1. Main Analysis Symptom Measures

The primary analysis population will include all participants randomised to a treatment arm, as defined by protocol eligibility criteria, regardless of what intervention they actually received or compliance with the intervention. Other analysis populations will be pre-specified

in the Statistical Analysis Plan (SAP), as appropriate. For reporting purposes, baseline/Visit 1 variables will be presented by treatment arm using frequencies (with percentages) for binary and categorical variables and means (and standard deviations) or medians (with lower and upper quartiles) for continuous variables. There will be no tests of statistical significance nor confidence intervals conducted for differences between groups on any baseline variables; the stratified randomisation program, *Sortition*, will use eligibility data from study enrolment.

The results from the RCT will be presented as comparative summary statistics (difference in proportions or means) with 95% confidence intervals. The statistical significance of all two-sided inferential tests examining differences between the treatment arms will be determined at a 5% significance level. The study results will be reported in accordance with the CONSORT 2010 statement and a full detailed statistical analysis plan (including any secondary, subgroup and sensitivity analyses) will be prepared before recruitment starts.

A mixed effect model will be fitted to the data with ITQ score at 9, 17, 26, 39, and 52 weeks as the dependent variable. The model will include a random intercept for each participant to account for the repeated measures on the same participant and an interaction term for the treatment by time interaction to allow the treatment effect to differ at each time point. Included in the model will be fixed effects for randomised groups, factors used at group randomisation, and any factors that are deemed to be highly prognostic to the outcome. Adjusted mean differences between the treatment groups in ITQ with 95% confidence intervals and p-values will be estimated from the model.

Missing data will be reported, with reasons where available, and the missing data mechanism explored. The mixed effect model implicitly accounts for data missing at random (MAR). Additional sensitivity analysis using imputation methods, such as multiple imputation for missing data, will be performed and a pattern mixture model for longitudinal data will be fitted to assess the robustness of the MAR assumption required for the mixed effect model. Further details for these *a priori* analyses will be specified in a separate statistical analysis plan.

11.1.2 Process Evaluation

A process evaluation conducted alongside the main trial will explore moderators of outcome and mediators of change. We will approach a subset of participants for verbal recorded consent to allow their therapy sessions to be audio and video recorded at the beginning, middle and end of the treatment period to assist us with our fidelity assessments and our process evaluation. Moderators to be considered include: comorbid depression; substance use; trauma type; childhood trauma; number of traumas re-experienced; mental defeat; ethnic group; education level; gender; treatment without/with interpreter; self-harm, self-criticism, fear of self-compassion; affect without recollection; and treatment credibility. Mediators of treatment outcome to be considered in the analyses are processes hypothesized to maintain PTSD (i.e. unhelpful appraisals, memory qualities, maintaining behaviours such as rumination and thought suppression or safety behaviours), self-criticism and working

alliance, using the following measures Posttraumatic Cognitions Inventory (PTCI), short version [47], Trauma Memory Questionnaire (TMQ), short version [48], Response to Intrusions Questionnaire (RIQ), short version [49], Safety Behaviours Questionnaire (SBQ), short version [50], Trait-State Dissociation Questionnaire (TSDQ), short version [50], Forms of Self-Criticising/Attacking and Self-Assuring Scale [51], Compassionate Resilience Scale (CRS), and Working Alliance Inventory (WAI, patient and therapist versions) [52] Effects of sleep disturbance/insomnia will also be considered here. Further details for these analyses will be specified *a priori* in a separate statistical analysis plan.

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11.1.3 Health Economic Evaluation

An economic evaluation will be performed alongside the clinical trial to assess the cost-effectiveness of phased CT-PTSD for the treatment of PTSD. Data on health-related quality of life (measured by the EQ-5D-5L questionnaire [44] and the ReQoL Scale [45]), use of health and social care services as well as productivity loss and informal care due to PTSD will be collected through an adapted version of the *Client Service Receipt Inventory* (CSRI, [46]) and iMTA Productivity Cost Questionnaire, short form (PCQ) [60] at baseline/Visit 1, 26, and 52 weeks. A costing template will be used to estimate the intervention costs per patient. Incremental cost-effectiveness ratios (ICERs) will be expressed in terms of cost per participant with a clinical improvement in PTSD symptoms and costs per quality adjusted life year (QALY) gained. QALYs will be calculated using the area under the curve method based on EQ5D-5L and ReQOL utilities. Bootstrapping with replacement will be used to construct cost-effectiveness planes in order to display uncertainty around the ICERs. The probability of phased CT-PTSD and non-phased CT-PTSD for the treatment of PTSD to be cost-effective at different willingness-to-pay values of a QALY will be displayed on cost-effectiveness acceptability curves. Heterogeneity within the data will be explored in subgroup analysis following the protocol of the clinical trial. Further details (*a priori* and potential post-hoc analyses) will be specified in a separate health economic analysis plan.

As reported in the NICE Guideline (NG116 [5]), there is no economic evidence on psychosocial or psychological interventions for the treatment of PTSD in adults: no economic analysis was undertaken by NICE during the development of the guidelines, and research in this area is much needed.

11.2 Number of Participants and Power Analysis

We plan to randomise 350 participants to a treatment arm using *Sortition*. Experience from previous trials suggests that we will need to assess about 470 patients for eligibility.

The trial has been powered to detect an effect size of Cohen's $d = 0.4$ for the comparison between phased CT-PTSD and non-phased CT-PTSD. This effect size was chosen as it corresponds to minimum differences in PTSD measures that are considered statistically

reliable in the literature. For example, a minimum difference of 5 is recommended for the PCL-5 [37] and standard deviations in samples of patients with complex PTSD [30] are in the region of 11 to 12, so a difference of 5 would be an effect size greater than 0.4. Similar results [57] are obtained for the ITQ [36].

To detect a difference with an effect size of $d = 0.4$ with 90% power at the 5% level of significance (2-sided), 132 participants per group are required for this RCT. In addition, we have allowed for effects of clustering of observations within therapists, assuming a conservative intra-class correlation of 0.01 (following Baldwin et al.'s recommendation [58]) and an average cluster size of 6, leading to a design factor of 1.05. Assuming the coefficient of variation is estimated to be 0.1, (we have conservatively allowed for 15% drop-outs, which is above the rate observed in two consecutive cohort studies of non-phased CT-PTSD [14]), the total sample required for this study is 350 (i.e., 175 per treatment arm).

11.3 The Level of Statistical Significance

Significance levels for hypothesis testing/tests of inference are set at $p < 0.05$ (two-tailed) for this RCT.

11.4 Criteria for the Termination of the Trial and Progression Criteria for internal pilot phase

The funding agreement stipulates an **internal pilot phase** before progression to full trial**.** After 6 months following the start of recruitment for the trial, we will assess a range of progression criteria for recruitment, retention, and treatment adherence and fidelity. Progression criteria are shown in Table 1. Definite progression requires a recruitment rate of 100% and drop-out rate below 15%. In the case of lower recruitment rates, we will review procedures and possibly enhance the number of therapists recruiting patients into the trial per site. The CIs will consider the replacement of sites who fail to recruit sufficient numbers of patients and/or additional recruitment at existing sites to meet the needs of the protocol and the statistical analysis plan.

In case of higher than expected drop-out rates, we will review the participants' reasons for dropping out and implement measures to reduce them (e.g. additional training for therapists or researchers; additional incentives).

If therapist adherence to treatment is lower than expected, the research centre will offer trial therapists additional therapist training and supervision. If patient adherence to treatment tasks is lower than expected, we will explore possible reasons with them and discuss possible solutions with them and PPI groups.

Table 1: Proposed length of internal pilot phase: 6 months

(February 2023 – July 2023)

	Red Do not progress to main trial	**Amber** (progress to main trial phase implementing strategies (e.g. additional therapists or additional sites)	**Green (Definite progress to main trial phase)**
Trial Recruitment			
Recruitment rate/site/month	< 60%	60% to 99%	100%, i.e., on average 2 patients per active site per month
Number of sites opened	< 60%	60% to 99%	100%, i.e., 10 sites active by end of pilot
Total number of participants recruited	< 60%	60% to 99%	100%, i.e., at least 80 patients recruited
Retention			
Drop-outs	>40%	15% to 40%	< 15%
Treatment Adherence			
Therapist adherence to treatment manual	<70%	70% to 99%	100%
Patient adherence to therapy tasks	<50%	50% to 80%	80%

11.5 Inclusion in Analysis

Analyses will be intent-to-treat (ITT), i.e. all participants randomised to a treatment arm will be included in the analysis.

12. DATA MANAGEMENT

12.1. Source Data

The PC-CTU data management team will be responsible for the data management of the trial in accordance to the Standard Operating Procedures (SOPs). A data management plan (DMP) will outline in detail the specific procedures that will be used to ensure high quality data will be delivered for statistical analysis and future use. The DMP will complement the trial risk assessment and statistical analysis plan. The DMP will cover data collection design/creation, database design and build, validation check design and build, data workflow, reporting requirements, query management, coding, data transfer, and database lock requirement. The research team and CTU will collect and store data in accordance with the study protocol. The research teams and participants at sites will directly enter data into a secured online database and inputs will be stored on a secure server at the CTU at University

of Oxford. The CIs and CTU will also prepare a data sharing policy that will provide details of how we will share data after completion of the trial.

Trial staff will ensure that participants' anonymity is maintained through good research design, by following the REC-approved protocol and their organisations' policies and procedures. The trial will comply with the Data Protection Act 2018/UK-GDPR, which requires research staff to anonymise research data and personal identifiers as soon as it is practical to do so. Researchers will identify participants by using the participant ID number randomised by *Sortition*, both on outcome measure paperwork and on any electronic trial database or external communication. The research teams at sites and the CTU will ensure personal information is kept separate from the trial research data at every stage.

In the event of source data being collected on paper (e.g. the ISI interview at baseline, 26, and 52 weeks), an exact copy of the anonymized data will be manually entered into the trial database by named study personnel, with the electronic data record being verified against the original paper record.

Authorised personnel will make any necessary changes to the data and a record of all authorised changes will be stored in the database audit log by these personnel.

12.2. Access to Data

Following notification, the CIs will grant direct access to the data to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13. QUALITY ASSURANCE PROCEDURES

The CIs will ensure the trial will be conducted in accordance with the current approved protocol, GCP, relevant policies and regulations and SOPs. Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol, completeness and accuracy in relation to source documents (for ITI).

The CIs (Dr Duffy, Professor Ehlers) will work closely with the PC-CTU regarding the overall management of the project. Professor Ehlers will liaise with the service leads in the English sites, who will oversee the recruitment in their respective services. Dr Duffy and Dr Mulholland will liaise with the service leads in the Northern Ireland sites, who will oversee the recruitment in their services.

A Trial Management Group (TMG) will oversee the day-to-day co-ordination and progress of the trial, managing any key issues and outstanding tasks requiring address.

14. TRIAL STEERING COMMITTEE

The Trial Steering Committee (TSC) will regularly view recruitment rates, compliance with the protocol, review of AEs/SAEs, and completeness of data collection. The members are independent experts specializing in clinical trials, PTSD or statistics (Professor Tim Dalgleish [University of Cambridge], Dr Patrick Smith [KCL]; Dr Mark McCann) and service user representatives (Mr. Paul Harte). The TSC will meet at least annually. TSC members will be required to sign up to the remit and conditions set out in the TSC Charter.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

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

15.2. Guidelines for Good Clinical Practice

The CIs will ensure that this trial is conducted in accordance with relevant NHS-E/HSC regulations and with ICH Good Clinical Practice (ICH GCP).

15.3. Approvals

The protocol, ICF (Part 1 and 2), PIS, PIL and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), and host institution(s) for written ethical and governance approval.
The CIs will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. The CIs will request support when seeking ethical and governance approvals across both UK nations, and will engage with their local Clinical Research Networks (CRNs), as needed.

15.4. Reporting

The CIs shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the REC, host organisation, any local assisting CRN and Sponsor. The CIs will note any additional support provided by CRNs in manuscripts and publications as part of their research dissemination plans.

15.5. Participant Confidentiality

The trial staff will ensure that participants' anonymity is maintained. The trial will comply with the Data Protection Act 2018/UK-GDPR, which requires data to be anonymised as soon as it is practical to do so.

Research Centre staff will store participant details and their GP contact details temporarily and separately from the trial data, on password-protected computers using secure University servers at the Queen's University Belfast and University of Oxford research centres for the sole purpose of ensuring the smooth running of the trial, and on NHS/HSC firewall protected systems at the research sites. The research site teams will access (using medical records and/or auditable ECRs) participant and GP contact details to facilitate any repeat contact activities for the purposes of this protocol. The files and accessible systems used in the research will be password-protected and accessible to trained delegated personnel in keeping with research governance procedures and organisational policies at the participating organisations.

Trial staff will identify participants by their participant ID number only on all research trial documents and on any electronic database containing research trial data.

The CTU will hold and store the Trial Master File (TMF) for 10 years after the end of the trial.

Trial staff will collect and store trial data using the secure REDCap database provided by the CTU. However, trial staff will identify any paper assessment forms in circulation (e.g. eligibility assessments and ITI interview data, any data gathered in remote clinical settings) and any paper-and-pencil questionnaires distributed (e.g. accessible translated versions of the forms) using the unique participant ID. These paper-based forms will be stored in Clinical Research Files (CRFs) in locked filing cabinets at sites (i.e. with any therapist trial records/logs) and/or in the trial administration offices at Queens University Belfast and University of Oxford centres, separate from participants' personal identifiable data, during the trial. Trial staff will add data from any paper-based assessment forms to participants' eCRFs within the online REDCap database at regular intervals (i.e. weekly) to facilitate transfer of data to the CTU for analysis purposes.

Raw audio and video files of ITI assessments, qualitative interviews or treatment sessions will be tagged using unique participant IDs prior to data extraction and analysis, and stored separately from other research and personal data on password protected computers and secure University servers at Queen's University Belfast and University of Oxford research centres. Staff and trial sites will be requested to use participant IDs in all communications regarding the RCT throughout the study period. The research team may opt to assign sites, raters, assessors and/or therapists with unique IDs following discussion with the CIs where this considered useful, practicable and judged to be improve practice by the research team.

After the end of the trial, any trial materials (e.g. copies of consent; therapists logs) present at trial sites will be reviewed for retention value, and with reference to organisational policies, will be retained for up to 10 years in secure archives before being destroyed.

15.6. Expenses and Benefits

Participants will be reimbursed £20 for their time for completing the trial assessments at baseline/Visit 1, 26 weeks and 52 weeks; and £10 for filling in questionnaires at 9 weeks (including some short additional questionnaires at 2 and 10 weeks), 17 and 39 weeks (see Appendix B).

Participants in the qualitative study will receive £30 for their time.

16. FINANCE AND INSURANCE

16.1. Funding

The trial is funded by NIHR HTA grant NIHR132705, awarded to Michael Duffy and Anke Ehlers.

16.2. Insurance

Queen's University Belfast has a specialist insurance policy in place that would operate in the event of any participant suffering harm as a result of their involvement in the research. This insurance in general provides cover for any claims that might be made against the University or its staff arising from a breach of professional duty.

17. PUBLICATION POLICY

The CIs will publish the results of the trial in peer-reviewed international journals within two years after completion of the study. In line with open access policies, the main publications will be made open access.

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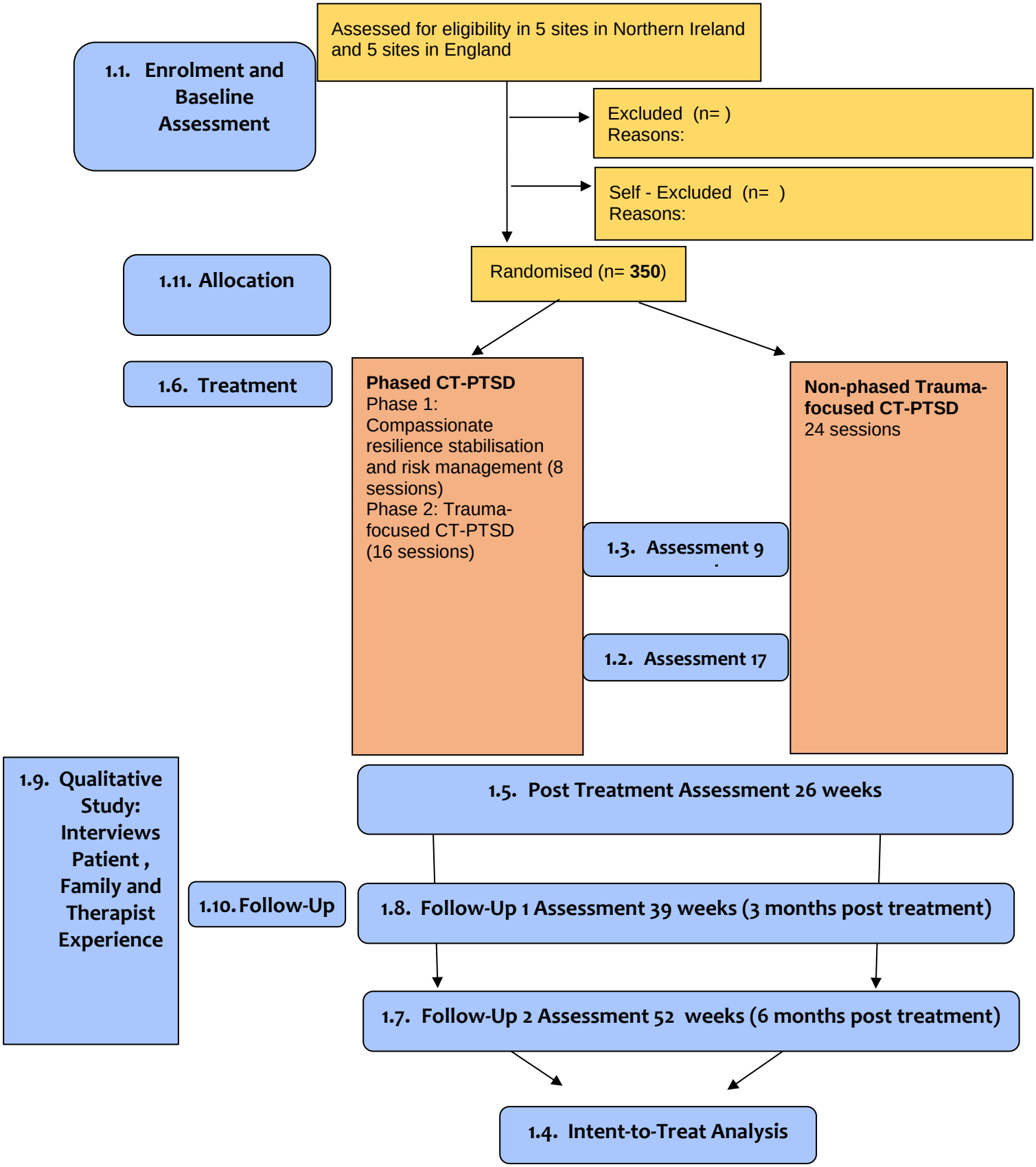
Appendix A: CONSORT Flow Diagram RCT Phased versus Standard TF-CT for PTSD



Appendix B: Assessment Schedule **TIMEPOINT**	**STUDY PERIOD**								
	Enrolment	**Allocation and Baseline Assessment**	**Treatment Phase**				**Follow-up**		
			During Treatment	**9 weeks**	**17 weeks**	**26 weeks**	**39 weeks**	**52 weeks**	
Participant Identification (in Services)									
Clinical assessment (incl. risk assessment & PDSQ)	X								
Eligibility Assessment (Research Team/Independent Assessor*)									
Informed consent for eligibility assessment	X								
Demographics & Medication Use (Patient Reg Form)	X								
International Trauma Interview (ITI)*	X					X		X	
Life Event Checklist (LEC)	X								
The Adverse Childhood Experiences Questionnaire, 11-item version (ACE-Q)	X								
Mental Defeat Scale (MDS)	X								
International Trauma Questionnaire (ITQ)	X	X	X***#	X	X	X	X	X	
Alcohol Use Disorders Identification Test (AUDIT)	X					X		X	
Medication use	X					X		X	
Informed consent for RCT	X								
Randomisation (stratified, minimization method)		X							
INTERVENTIONS (Therapists at the sites)									
Phased CT-PTSD			◆——	——	——	——◆			
Non-phased CT-PTSD			◆——	——	——	——◆			
ASSESSMENTS (Research Team) **Outcomes: Further Symptom and Well-Being Measures**									
PTSD Checklist for DSM-5 (PCL-5)		X	X***#	X	X	X	X	X	
Patient Health Questionnaire (PHQ-9)		X	X***	X	X	X	X	X	
Generalized Anxiety Disorder Scale (GAD-7)		X	X***	X	X	X	X	X	
Work and Social Adjustment Scale (WSAS)		X	X***	X	X	X	X	X	
WHO (Five) Well-Being Index		X		X	X	X	X	X	

Endicott Quality of Life (QoL) Scale		X		X		X	X	X	
IAPT Patient Experience Questionnaire (PEQ)						X			
Health Economic Measures									
EuroQoL EQ-5D-5L		X				X		X	
Client Service Receipt Inventory (CSRI)		X				X		X	
Recovering Quality of Life (ReQoL) Scale		X				X		X	
Employment status and state benefits Items		X				X		X	
Treatment delivery cost/ Treatment Record (therapist)			X#						
iMTA Productivity Cost Questionnaire, short form (PCQ)		X				X		X	
Therapy Process Measures									
Posttraumatic Cognitions Inventory (PTCI)		X	Monthly**	X	X	X	X		
Trauma Memory Questionnaire (TMQ)		X	Monthly**	X	X	X	X		
Response to Intrusions Questionnaire (RIQ)		X	Monthly**	X	X	X	X		
Safety Behaviours Questionnaire (SBQ)		X	Monthly**	X	X	X	X		
Trait-State Dissociation Questionnaire (TSDQ)		X	Monthly**	X	X	X	X		
Forms of Self-Criticising/Attacking and Self-Reassuring Scale (FSCRS)		X	Monthly**	X	X	X	X		
Compassionate Resilience Scale (CRS)		X		X		X			
Affect without Recollection Scale		X		X		X			
Working Alliance Inventory (WAI)			2 weeks 10 weeks						
Insomnia Severity Index (ISI)		X				X		X	
Treatment Credibility Credibility/Expectancy Scale (CES)			2 weeks 10 weeks						
(Serious) Adverse event/effect (AE/SAE) monitoring			X	X	X	X	X	X	

*** these measures are standard measures in the participating services, given weekly in IAPT services and monthly in other services

** these measures are used by therapists to plan treatment and are given routinely in CT-PTSD to monitor progress;

these measures will be collected weekly by the therapists to monitor progress in treatment and record duration and content of sessions

APPENDIX C: QUESTIONNAIRES & ACCOMPANYING STUDY DOCUMENTS

No.	Title	Version	Version & Date of Protocol
1	Patient Registration Form - Clinical assessment incl. risk assessment, demographic and medication use*	1.0*	
2	Psychiatric Diagnostic Screener Questionnaire [PDSQ; 59]		
3	Life Events Checklist (LEC) [34]		
4	The Adverse Childhood Experiences Questionnaire, 11-item version (ACE-Q) [61]		
5	Mental Defeat Scale (MDS) full scale 11 items [20]		
6	International Trauma Interview (ITI) [32]		
7	International Trauma Questionnaire (ITQ) [36])		
8	Alcohol Use Disorders Identification Test (AUDIT) [35])		
9	PTSD Checklist for DSM 5 (PCL-5) [37]		
10	Patient Health Questionnaire (PHQ-9) [38]		
11	Generalised Anxiety Disorder Scale (GAD-7) [39]		
12	Work and Social Adjustment Scale (WSAS) [40]		
13	WHO (Five) Well-Being Index [41]		
14	Endicott Quality of Life (QoL) [42]		
15	IAPT Patient Experience Questionnaire (PEQ) [43]		
16	EuroQoL EQ-5D-5L [44]		
17	Client Service Receipt Inventory (CSRI) [46]		
18	Recovering Quality of Life (ReQoL) Scale [45]		
19	Employment status and state benefits items*		
20	Treatment delivery cost (number of minutes of therapy) record sheet*		
21	iMTA Productivity Cost Questionnaire, short form (PCQ) [60]		

22	Posttraumatic Cognitions Inventory (PTCI), short version [47]		
23	Trauma Memory Questionnaire (TMQ), short version [48]		
24	Response to Intrusions Questionnaire (RIQ), short version [49]		
25	Safety Behaviours Questionnaire (SBQ), short version [50]		
26	Trait-State Dissociation Questionnaire (TSDQ), short version [50]		
27	Forms of ssing/ Attacking and Self-Reassuring Scale (FSCRS) [51]		
28	24a. Working Alliance Inventory (WAI) [52]		
29	24b.WorkingAlliance - Therapist_[52]		
30	Insomnia Severity Index (ISI) [53]		
31	Credibility Rating Scale (patient) – CES [54]		
32	Participant [Patient] Information Sheet_V1.0	1.0*	
33	Participant [Patient] Consent Form_V1.0	1.0*	
34	Participant [Therapist] Information Sheet_V1.0	1.0*	
35	Participant [Therapist] Consent Form_V1.0	1.0*	
36	Participant [Family member/Partner] Information Sheet_V1.0	1.0*	
37	Participant [Family member/ Partner] Consent Form_V1.0	1.0*	
38	Participant Interview Schedule	1.0*	
39	Therapist Interview Schedule	1.0*	
40	Family member/Partner Interview Schedule	1.0*	
41	Serious Adverse Event Template	1.0*	
42	Medication Review Form	1.0*	
43	Compassionate Resilience Scale	1.0*	
44	Affect without Recollection Scale	1.0*	
45	Letter to GP	1.0*	

*Unpublished items