# 1. Protocol details

## 1.1 Protocol title

Efficacy and mechanisms evaluation of remotely delivered Fast Imagery Reversal Script for Trauma release Protocol (FIRST Protocol) vs Waiting List (WL) Controlled group for Post-Traumatic Stress Disorder (PTSD) in UK military veterans (FIRST PETT)

## 1.2 Trial identifiers

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| ISRCTN: | TBC | | |
| REC Number: | HR/DP-23/24-41529 | | |
| UKCRN Number: | n/a | | |
| Protocol Version Number: | 1.0 | Date: | 23/04/2024 |

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## 1.6 Study Synopsis

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| Title Of Clinical Trial: | Efficacy and mechanisms evaluation of remotely delivered Fast Imagery Reversal Script for Trauma release Protocol (FIRST Protocol) vs Waiting List (WL) Controlled group for Post-Traumatic Stress Disorder (PTSD) in UK military veterans |
| Protocol Short Title/ Acronym: | FIRST PETT |
| Study Phase if not mentioned in title: | Phase 3 |
| Sponsor Name: | King's College London |
| Chief Investigator: | Professor Jackie Sturt |
| UKCRN Number: | TBC |
| REC Number: | TBC |
| Medical Condition Or Disease Under Investigation: | Post-Traumatic Stress Disorder |
| Purpose Of Clinical Trial: | Evaluate the efficacy and mechanisms of remotely delivered Fast Imagery Reversal Script for Trauma Release Protocol (FIRST Protocol) vs Waiting List (WL) Controlled group for PTSD in UK military veterans |
| Primary Objective: | Determine the efficacy of FIRST compared to wait list control at 20 weeks for achieving a Minimal Clinically Important Difference in PTSD symptoms. |
| Secondary Objective(s): | -Establish proof of concept of the remotely delivered FIRST protocol.<br>- Understand the impacts of FIRST on mental health and wellbeing.<br>-Understand 52-week FIRST maintenance of effect.<br>-Determine whether the mechanistic pathways can be understood through established cognitive science of PTSD. |
| Trial Design: | Parallel group single masked (outcome assessor) 1:1 randomised controlled superiority trial |
| Endpoints: | **1.6.1 Primary endpoints**<br>1) PTSD symptom severity assessed by the PCL-5.<br>**1.6.2 Secondary endpoints**<br>1) PTSD diagnosis assessed by the CAPS-5.<br>2) The impact of the person's mental health on work, home, social and private leisure activities and |

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| | interpersonal relationships assessed by the *Work and Social Adjustment Scale.*<br>3) Depression assessed by *The Patient Health Questionnaire (PHQ9).*<br>4) Health status assessed by *The EQ5D-5L.*<br>5) Self-rated self-esteem assessed by *The Self-esteem scale.* |
| Sample Size: | 215 |
| Summary Of Eligibility Criteria: | •UK based military veterans from the Royal Navy or Royal Marines, British Army, Royal Air Force<br>•Male and female military veterans ≥18 years<br>•Ability to read and speak English<br>•Experiencing clinically important symptoms of PTSD of >32 on the PCL5<br>•Self-reported history of exposure to one or more traumas<br>•Willingness to be randomised to treatment group<br>•Willingness for the therapy sessions to be video recorded |
| Intervention (Description, frequency, details of delivery) | FIRST is a brief intervention delivered in 3 to 4 x 90-120 minute sessions by a FIRST therapist via videocall. FIRST rewrites the emotional elements of the memory. FIRST therapy will be delivered over a minimum of three days and a maximum of four weeks. The two factors determining this are a) there must be one sleep cycle between each therapy session and b) scheduling of therapy sessions for the participant and the therapist. The FIRST protocol incorporates 18 steps in five stages: a) Pre- randomisation assessment by DES; b) Priming process; c) Desensitisation process through dissociation; d) Undoing of trauma memory through reversed imagery; e) Reconsolidation. Therapy sessions will be delivered remotely, and our therapy delivery and clinical governance partner and collaborator is Inspire; a mental health charity located in Northern Ireland (https://www.inspirewellbeing.org/) who delivered all therapies remotely in the feasibility trial. Inspire therapists are experienced in working remotely with cross-UK and Republic of Ireland military veterans since online mental health assessment and therapy became mainstream therapeutic provision during the COVID-19 pandemic. For an efficacy trial this third sector organisation offers a more *ideal setting* for the following reasons: a) the flow of participants through the trial is controllable because there are many fewer competing interests than within the NHS; b) Inspire, due to their Northern Ireland location, have considerable expertise in working with military veterans and other populations with occupationally-related PTSD; and c) they have robust clinical governance procedures which are adaptable to being supplemented with FIRST |

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| | therapy-specific clinical supervision. |
| Comparator Intervention: | Waiting List |
| Maximum Duration Of Treatment Of A Subject: | Four weeks |
| Version And Date Of Final Protocol: | V1.0 23-04-24 |
| Version And Date Of Protocol Amendments: | |

### 1.7 Revision History

| Document ID - (Document Title) revision X.Y | Description of changes from previous revision | Effective Date |
|---|---|---|
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## 2 Table of Contents

## 3 List of Abbreviations

AMT Autobiographical Memory Task

ARM-5 Agnew Relationship Measure – 5

AUDIT Alcohol Use Disorders Identification Test

BABCP British Association of Behavioural and Cognitive Psychotherapy

BACP British Association for Counselling and Psychotherapy

CAPS5 Clinician Assessed PTSD Scale

CBT Cognitive Behaviour Therapy

CERQ Cognitive Emotion Regulation Questionnaire

CI Confidence Internals

CPTSD Complex Post Traumatic Stress disorder

DBS Disclosure and Baring Service

DES-II Dissociative Experiences Scale- II

DMS-5 The Diagnostic and Statistical Manual of Mental Discorders, 5th edition

EMDR Eye Movement and Desensitisation and Reprocessing

*EQ5D-5L* European Quality of Life Five Dimension-Five Levels

FIRST Fast Imagery Reversal Script for Trauma

GDPR General Data Protection Regulation

GP General Practitioner

HCPC Health Care Professions Council

IAPT Improving Access to Psychological Therapies

ICD-TQ International Trauma Questionnaire

ICP Irish Council for Psychotherapy

IP Intellectual property

ISRCTN Internation Standard Randomised Controlled Trial Number

KCL King's College London

KCTU King's College London Clinical Trials Unit

M Month

MCID Minimal Clinically Important Difference

NCPS Acc National Counselling and Psychotherapy Society, Accredited Professional Registrant

NHS National Health Service

NI Northern Ireland

NICE National Institute for health and Clinical Excellence

NLP Neurolinguistic programming

NLPt Neurolinguistic programming techniques

PCI-9 Post-traumatic Cognition Inventory Scale

PCL-5 Post-traumatic Stress Disorder Checklist for DSM-5

PETT PTSD Experimental Treatment Trial

PHQ9 *The Patient Health Questionnaire -9*

POC Proof of Cobcepot

PPI/PPIE Public and patient Involvement and Engagement Group

PROMS Patient Reported Outcome Measures

PSSI *Psychometric properties of the Posttraumatic Stress Disorder Symptom Scale Interview for DSM–5*

PTSD Post Traumatic Stress Disorder

RCT Randomised Controlled Trial

REC Research Ethics Committee

RTM Reconsolidation of Traumatic memories

SAP Statistical Analysis Plan

SD Standard Deviation

TF-CBT Trauma Focussed Cognitibve behaviour Therapy

TMQQ The Trauma Memory Quality Questionnaire

UK United Kingdom

UKCRN United Kingdom Clinical Research network

UKCP United Kingdom Council of Psychotherapy

US United States of America

VM Verbal memory

WL Waiting List

WMP Working memory performance

*WSAS Work and Social Adjustment Scale*

WWTW Walking with the Wounded

# 4 Summary

## 4.1 Aims and objectives are to

1 Establish proof of concept of the remotely delivered FIRST protocol.
2 Determine the efficacy of FIRST compared to wait list control at 20 weeks for achieving a Minimal Clinically Important Difference in PTSD symptoms.
3 Understand the impacts of FIRST on mental health and wellbeing.
4 Understand 52-week FIRST maintenance of effect.
5 Determine whether the mechanistic pathways can be understood through established cognitive science of PTSD.

## 4.2 Trial hypothesis and PICOT

In UK military veterans (P) the remotely delivered FIRST Protocol (I) compared to waiting list control (C) is clinically and statistically effective in reducing PTSD symptoms by the minimal clinically important difference (O) at 20 weeks (T).

## 4.3 Background

Post-Traumatic Stress Disorder (PTSD) is a mental health condition which can follow experiencing, or witnessing, events such as threatened or actual death, serious injury or sexual violence. PTSD rates in the general population are 4% but in military veterans it can be up to 17% or higher. For up to 80% of veterans, their PTSD is Complex associated with multiple, or prolonged, traumas. Some veterans find it difficult to seek NHS therapy because it is lengthy and requires trauma recall. NHS therapies are costly which limits availability. Charities and policy makers agree that new PTSD therapies are called for that better meet veterans' needs. Neurolinguistic programming (NLP) offers brief therapy interventions for people with mental health symptoms, easily delivered by novice psychological care professionals. Several small studies have shown proof of concept but because it is viewed with suspicion by the psychology community no efficacy evidence exists nor little understanding of mechanisms by which it achieves its effects. Understanding mechanistic pathways will help to integrate these brief interventions into standard mental healthcare. The FIRST protocol incorporates NLP and theoretical reconsolidation techniques targeting PTSD symptoms.

## 4.4 Methods

The trial is a patient-level 1:1 computer randomised controlled trial preceded by a single arm proof of concept study. The trial incorporates a five-month internal pilot, a nested mechanistic experimental study and 52-week maintenance of effect analysis. Over 20 months we will recruit 215 UK military veterans with PTSD and randomise them to immediate FIRST therapy or five-month waiting list control. FIRST is delivered online via trained, supervised, charity partner therapists. Primary trial outcome is PTSD symptoms assessed by the PCL-5. Cognitive outcomes align with mechanistic hypotheses. The final trial follow-up on all outcomes is 20-weeks.

## 4.5 Timelines for delivery

This is a forty-eight-month (M) trial: M 1-6 are set up, training and KCL ethical approval. M7-12 is proof of concept. The trial commences M 14 with internal pilot and reporting (M 14-18 and recruitment, randomisation and baseline data collection continuing to M 32. Therapy delivery and final 20-week follow up data collection M 15 to 38. Data analysis and maintenance of effect data collection M 39-46. Reporting and dissemination concludes M 47-48.

## 4.6 Anticipated impact and dissemination

Determining the efficacy and mechanisms of FIRST can lead to significant opportunities for upscaling therapist training and PTSD treatment across NHS. Dissemination will target NHS England and Improving Access to Psychological Therapies (IAPT) services for treatment upscaling.

# 5 Background

## 5.1 PTSD and NHS therapy for military veterans

PTSD is a psychiatric disorder resulting from experiencing or witnessing traumatic events such as threatened or actual death, serious injury or sexual violence [1]. Around 17% of combat military veterans experience PTSD; this rate may be as high as 37% in veterans living in Northern Ireland. This compares to around a 4% PTSD prevalence in the general English population [2, 3]. There are 2.4 million veterans in the UK, equating to 425,000 veterans living with PTSD [4]. People aged 70+ account for 50% of UK veterans [5]. Ethnic minority veterans make up 2.3% of the veteran population [5]. Women currently make up 13.6% of the veteran population [5] and this is expected to grow to 13% by 2028 [6]. Despite this just 2% of the veteran research mentions women and even smaller proportion focuses on women as the primary source [7].There is only partial overlap between the traumatic events reported by female veterans and those reported by males. In particular, sexual trauma is more commonly reported by female veterans (during- and pre-military) [8]. The prevalence of PTSD is marginally higher in women veterans although the nature of the PTSD symptoms are comparable with male veterans [3, 8]. Women veterans are less likely to receive a PTSD diagnosis when sexual trauma is a causative factor [8, 9]. PTSD adversely impacts social functioning, including homelessness, physical health problems, and frequently is associated with mental health comorbidities such as substance misuse and suicidality [1, 10-12]. 80% of veterans with PTSD also have Complex-PTSD (CPTSD) resulting from multiple traumas [13]. Chronic PTSD is unlikely to resolve spontaneously, and the risks of adverse outcomes increases if untreated [14]. Current NICE recommended therapies for PTSD in veterans are Trauma-Focussed CBT (TF-CBT) and Eye Movement Desensitisation and Reprocessing (EMDR) [1, 15], although EMDR is not recommended for combat-related PTSD. Both treatments, whilst cost-effective, have important limitations. Both typically require between 8 to 18 sessions for optimal efficacy [16] and are extensive and time-consuming; resulting in limited NHS-based therapist numbers causing potentially lengthy treatment waiting lists. The trauma-focussed nature of both TF-CBT and EMDR leads to treatment dropout in research studies of up to 58% [17] while non-response treatment rates to TF-CBT in veterans can be as high as 50% [15, 18]. Given the scale of the problem of PTSD in veterans, and the practical challenges of providing timely, evidence-based therapy for PTSD, there is a pressing need for accessible, cost- and time effective treatments.

## 5.2 Neurolinguistic programming therapies (NLP) in third sector organisations

Veterans often turn to veteran charities for mental healthcare. Many of these charities utilise NLP approaches which promise symptom reduction in fewer treatment sessions using therapeutic protocols which can be provided by less experienced therapists [19]. NICE recognises the potential of some of these therapies [1] which have been developed under the umbrella of NLP and whilst evidence for proof of concept is developing [20, 21] efficacy evidence to inform widespread use is absent. Since its early development in the 1970s [22, 23] NLP has been viewed as pseudoscience resulting in limited quality evaluations. NLP is a communication framework using techniques to understand and facilitate change in thinking and behaviour [19]. It has been strongly criticised in academic and clinical psychology for lack of theory and little robust clinical evidence on which to base bold claims [19]. Much of this criticism over the past 40 years is associated with the lack of theory and experimental science to support an understanding of the mechanisms of its action [24]. In an attempt to claim ownership of NLP, the United States (US) High Court found that no-one has exclusive right to its use because it is a concept, a way of thinking, and any person in the field may train others (see Intellectual Property Disputes section of Neuro-linguistic programming - Wikipedia). Proof of concept studies using NLP and reconsolidation techniques in US veteran populations, and one led by this team in UK military veterans clinically indicates an efficacy signal for PTSD symptom reduction in 3-5 treatment sessions [20, 25, 26]. The efficacy signals for men and women are comparable [26]. In a webinar with veteran charity stakeholders and in four PPI group meetings involving veterans who participated in the feasibility study we were told that new treatments for PTSD are needed that are shorter, non-traumatising, available, acceptable and can be delivered within the veteran charity sector.

### 5.3 Fast Imagery Reversal Script for Trauma release Protocol (FIRST Protocol)

Our proposed intervention incorporates 1) concepts from the body of NLP that have demonstrated proof of concept [20, 21, 25], 2) reconsolidation processes [27], and 3) established neurocognitive techniques (FIRST is described fully in the Intervention section). NLP and reconsolidation therapies have been used to treat PTSD symptoms and found to be efficacious in several populations including veterans [20, 26-30]. FIRST protocol is novel since it a) avoids detailed recounts of trauma and therefore impacts positively on treatment retention and completion rates b) reduces re-traumatisation and c) is delivered in 3-4 face-to-face or online sessions of 90-120 minutes with at least one sleep cycle between sessions [31]. Compared to NICE recommended treatments, FIRST is delivered in approximately one quarter of the number of sessions, while therapist training requires 3.5 days, including pre course work, compared to several years of post-graduate study for TF-CBT training which could reduce treatment waiting times. Together, these elements potentially offer PTSD treatment upscaling and significant cost-saving advantages.

The theory of reconsolidation is an important component of FIRST. Reconsolidation proposes that an existing trauma memory can be destabilised after memory activation and re-stabilised during an open, time-dependant, window where new information can be integrated into an existing memory [32-34]. It theoretically weakens the original fear memory [33] which prevents the traumatic/fear memory from being recoverable. The theory of reconsolidation is an important, possible, mechanistic pathway for FIRST [31, 35], however, there may be existing, well researched, PTSD mechanistic pathways that may contribute an explanation to how reconsolidation, and FIRST overall, may assert its effect. Studies of other reconsolidation protocols [20, 21, 36] shows evidence changes in PTSD symptoms but to date there has been little research to understand whether well-established neurocognitive concepts contribute to symptom improvement in these therapies. By understanding the neurocognitive mechanisms, we propose that the FIRST protocol could be advanced further to target specific trauma presentation.

### 5.4 FIRST therapeutic mechanisms

Well-evidenced neuropsychological mechanisms explain the effectiveness of other psychological therapies for PTSD (e.g. CBT, EMDR, TF-CBT). Therapeutic alliance is also already a well-recognised mechanistic phenomenon and is made up of bond, partnership, confidence and openness [37].Treatment duration also plays a role but in our brief intervention it is less likely to. Effectiveness of therapeutic alliance in brief therapy provided via videoconferencing is also established [37, 38]. This is the first study examining NLP and neurocognitive mechanisms of change of the FIRST protocol. Memory related models offer psychological explanations for the development and maintenance of PTSD, and they specifically focus on how traumatic events are being maintained in long-term memory [39], while current interventions focus on how to improve memory related diagnostic criteria for PTSD. Studies have established verbal and non-verbal memory [40] deficits including poor information encoding, retrieval and recognition in veterans with PTSD [40, 41]. The main idea is that long-lasting traumatic experiences alter the structure, the function and the processing of memory contents [39]. FIRST improves veterans' ability to consciously remember and reproduce emotionally free neutral memories related to the traumatic event. Intrusive memories are manipulated via a twice or doubly dissociated position and become emotionally neutralised and can therefore be processed without triggering PTSD symptoms.

In PTSD, an *inability to suppress fear responses* results in long lasting symptoms [42]. Fear extinction is achieved by the genesis of new memories and not by erasure of the initial fear conditioned association (trauma experiences) [42] . In people with PTSD, the ventromedial prefrontal cortex which modulates memory or recall of extinction, shows morphological and functional abnormalities, suggesting that extinction circuits are compromised [43]. FIRST helps veterans to alter visual-sensory processes and have the ability to resist interference from distracting stimuli which improves neuropsychological symptoms.

*Imaginal exposure techniques* focuses on recalling traumatic events in detail, while focusing attention on any occurring sensory feeling, thought and emotion and is an evidence based, well-established technique for treating PTSD [44] . The presumed underlying mechanism is the loosening of the association between unconditioned and conditioned stimuli [45, 46]. In FIRST, imaginal exposure does not require the person to recount in any detail the traumatic memory -

which reduces re-traumatisation - and supports veterans to reduce fear memory and avoidance of the traumatic experience.

*Information-processing theory* proposes that stimulus-response information and their meanings, are stored in fear networks. The fear memory must be activated, and new information that is incompatible with the current fear structure must be provided [45]. The method helps the traumatic imagery to correct the situation in fantasy, and to produce a more favourable outcome - a key process in FIRST. Therefore, Veterans regain control and re-establish power over the traumatic event and improve their ability to regulate their emotions; a key mechanism of change in current psychological interventions for PTSD [47]. In FIRST, imaginary rescripting requires removal of the perpetrator from the imaginary movie and in some instances deletion of the event, as if it never happened. The effects of rescripting were also evidenced in our feasibility trial [25]. PTSD patients often exhibit disturbances in *self-referential processing* [48] . Negative attributions to emotions, such as perceptions that an emotion is problematic, aversive, or unacceptable, can affect self-perceptions following the traumatic event. Cognitive perceptions and emotions are a key mechanism of change for PTSD [47] . FIRST facilitates alterations in self-evaluation by modifying the self-appraisal and self-attributions after the trauma. Our feasibility study revealed that Veterans' self-esteem was improved, and they adopted a neutral and at times better perspective of self and the traumatic experience. FIRST improves self-perceptions and non-trauma specific symptoms such as self-esteem.

Evidence demonstrates impaired working memory [49, 50], greater distraction by external stimulus, worse attentional control [51] and worse attention disengagement from negative stimulus [52] in PTSD. Kangaslampi & Peltonen (2022) review revealed that *attentional processes* are potential mechanisms of change in PTSD, however more evidence is needed [47]. Modifying attention towards task-related stimuli and/or far away from threat related stimuli improves working memory and PTSD symptoms. FIRST proposes two elements that improves attentional process by increasing environmental cues and a significantly limiting attention exposure to threatening stimuli and interrupting all fear potentiating startle responses as soon as hyper arousal is observed.

We believe understanding mechanistic pathways will help to integrate FIRST into standard PTSD care and optimise therapeutic change by enabling targeting of specific mechanisms for maximising FIRST's effects. Our mechanistic hypotheses have been developed with reference to the PTSD neuroscience, a deep understanding of the FIRST protocol and qualitative interviews with feasibility trial participants.

### 5.5 Review of existing evidence

A meta-analysis examining the effects of reconsolidation/consolidation therapies for prevention and treatment of PTSD and symptoms [27] found a large effect. Our ongoing evidence review of the most evaluated reconsolidation approach (PROSPERO no CRD42021240398) identified four studies meeting the inclusion criteria [20, 26, 28, 30] and two under peer review [29, 53]. Participants (n=274) were all US residents with PTSD diagnoses, 64% male, 49% had military-related traumas. Study designs were RCTs with wait-list controls (x5) and pre-post (x1) with sample sizes ranging from 25-85 and follow up ranging 6 to 12 months. Meta-analysis of four studies assessing PTSD symptom scores using several different validated scales such as the PCL-5, CAPS 5 and PSSI [54-56] at two weeks post treatment showed a treatment effect favouring the reconsolidation group ($Z=20.43$, $P< 0.00001$, $I2=19\%$). At six weeks, treatment completers had a symptom reduction of 33.07 (SD= 5.854) points from baseline with over 90% losing their diagnosis at one year. Mean duration of therapy delivery was three weeks, delivered in three sessions. A high or unclear risk of bias was identified. In March 2022, we completed a 60-participant UK feasibility trial of a protocolised, online delivered reconsolidation therapy called RTM compared to online delivered TF-CBT in military veterans replicating the meta-analysis efficacy signal [25]. Veterans' mean age was 53 years, mostly male, white-British and in long term relationships. All ranks and services were represented with greater proportions from the lower ranks, 46 had served for five years or more and 30 had been deployed overseas ≥3 times. The mean baseline PTSD symptom score on the PCL-5 [54] was 57 (14 points above diagnostic threshold), 50 had complex PTSD and 39 had experienced ≥4 traumas. The final endpoint for the feasibility study was 20 weeks. At 20 weeks the signal of effect outcome was a 10-point minimal clinically important

difference (MCID) in PTSD symptoms assessed using the PCL-5 [57]. The experimental therapy experienced a mean 18-point reduction on the PCL-5 compared to an 8-point reduction in TF-CBT group. Loss of diagnosis was found in 49% of the experimental group versus 16% in the TF-CBT group [25]. The trial met the majority of the pre-specified progression criteria including recruitment, randomisation, lost to follow up, completeness of outcome data, PCL-5 outcome at 20 weeks and compliance with therapy [25].

In our feasibility trial we included a further endpoint, secondary to the primary 20-week endpoint, at 52-weeks post randomisation. The results showed a positive signal for PCL-5 scores after treatment with the proposed novel intervention. The mean 52-week PCL-5 score was 40.52 (SD=14.48; RTM) compared to 47.33 (SD=12.66; TF-CBT), while the mean change from baseline to 52 weeks showed a reduction of 15.16 (SD=16.00; RTM) compared to 7.93 (SD=13.17; TF-CBT). Finally, 62.07% participants met the minimal clinically important difference for the PCL-5 measurement (95% CI 42.76, 78.18; RTM) which compared to 46.67% (95% CI 22.38, 72.64; TF-CBT). Depressive symptoms at 52 weeks, assessed by the PHQ-9, was 15.00 (SD=5.74; RTM) compared to 16.93 (SD=5.02; TF-CBT), while the mean change from baseline to 52 weeks showed a reduction of 2.93 (SD=5.33; RTM) and 3.71 (SD=6.79; TF-CBT). Finally, 35% (95% CI 19.12, 53.95) RTM participants met the minimal clinically important difference for PTSD symptom reduction compared to 27% ((95% CI 9.42, 55.99) for TF-CBT. One year trial endpoint evidence in PTSD populations is limited. Mavranezouli et al (2020) published a systematic review and meta-analyses of 90 trials, involving 6560 individuals and 22 psychological interventions for adults presenting with PTSD [58]. TF-CBT was found to be the most effective therapy, however effectiveness was only measured to four months. The authors summarised that follow up data beyond four months was very sparse for both PTSD symptom change and remission. Evidence from three TF-CBT trials published subsequently and analysed for patterns and predictors of PTSD symptom change in war-related veterans found that substantive change that occurred over the course of treatment was maintained to 12 months [59]. Together with our own 52-week RTM evidence this demonstrates there is a need for more, longer therapy, trials but these pose challenges which might account for the sparsity of longer follow up evidence. Comparing an experimental therapy to a control (no therapy) condition has significant ethical considerations that need to be managed carefully. The longer the end point, the greater the participant safety risk. A second challenge is the cost of delivering a therapy comparison trial when the therapy comparisons (i.e. TF-CBT) are costly due to duration of therapy and therapist training.

Qualitative data from the feasibility trial found the study's procedures and treatments acceptable to veterans. The experimental reconsolidation group reported altered understanding of trauma and that therapy provided a new perspective for interpreting their trauma. Anger, stress, irritability, mood and emotional regulation, motivation and mental health also improved. We have incorporated modifications following the feasibility evaluation detailed in the project plan and section 3 (changes from stage 1) and in discussion with our PPI group.

# 6 Methods

## 6.1 Aims and objectives are to:

1) Establish proof of concept of the remotely delivered FIRST protocol.
2) Determine the efficacy of FIRST compared to wait list control at 20 weeks for achieving a Minimal Clinically Important Difference in PTSD symptoms.
3) Understand the impacts of FIRST on mental health and wellbeing.
4) Understand 52-week FIRST maintenance of effect.
5) Determine whether the mechanistic pathways can be understood through established cognitive science of PTSD.

## 6.2 Trial hypothesis and PICOT

In UK military veterans (P) the remotely delivered FIRST Protocol (I) compared to waiting list control (C) is clinically and statistically effective in reducing PTSD symptoms by the minimal clinically important difference (O) at 20 weeks (T).

### 6.3 Primary endpoints

1) PTSD symptom severity assessed by the PCL-5.

### 6.4 Secondary endpoints

1) PTSD diagnosis assessed by the CAPS-5.

2) The impact of the person's mental health on work, home, social and private leisure activities and interpersonal relationships assessed by the *Work and Social Adjustment Scale.*

3) Depression assessed by *The Patient Health Questionnaire (PHQ9).*

4) Health status assessed by *The EQ5D-5L.*

5) Self-rated self-esteem assessed by *The Self-esteem scale.*

## 7 Mechanisms study

Objective: To test hypotheses for the FIRST protocol's mechanistic pathways by which it achieves its effects.

Hypothesis: The amelioration of one or more of the proposed mechanistic outcomes will align with a reduction of PTSD and CPTSD symptoms found in the trial outcomes.

The impact of understanding mechanisms is that NHS and other therapists can be confident in using the FIRST protocol to treat PTSD and CPTSD and it should be rolled out in treating the veteran and other PTSD populations. Furthermore, if these mechanisms explain the causal pathway by which the FIRST protocol achieves effective reduction of PTSD and CPTSD symptoms, then it follows that FIRST can be implemented in populations who do not meet PTSD and CPTSD criteria but nonetheless have a trauma history and have distressing PTSD symptoms. Specific mechanistic hypothesis at the psychological and symptom level are discussed below and visually presented in table 1 and figure 1.

### 7.1 Mechanisms pathway

The study aims to test two domains of mechanistic pathways for the FIRST protocol: a) cognition and b) quality of memories.

People experiencing PTSD, and CPTSD, report maladaptive appraisals towards themselves (negative self-concept) which increases the number, and severity, of PTSD symptoms, and particularly those related to shame, guilt, dissociation [60] and dysfunctional cognitions about oneself in relation to the traumatic event [61, 62]. Current literature on mechanisms of well-established trauma related interventions identifies that changing maladaptive appraisals is an important constituent of a positive treatment outcome [63]. We hypothesise that changes in maladaptive appraisals towards oneself (negative self-concept) is also a key cognitive mechanistic pathway for the FIRST protocol. In addition, veterans with PTSD/CPTSD exhibit more temporal fluctuations in self-esteem, negative affect, and gratitude, with a smaller effect for positive affect compared to veterans without PTSD; this diminishes their well-being [64]. Our study's qualitative data demonstrated that self-esteem could be a potential non-trauma related outcome after treatment [25]. Therefore, we first hypothesise that cognitive mechanisms pathway for the FIRST protocol involves changes in maladaptive appraisals towards oneself resulting in reduced PTSD symptomatology (guilt/shame/dissociation/dysfunctional cognitions).

Veterans with PTSD present higher rates of impulsive and emotionally charged, uncontrolled, aggression and hostility compared to veterans without PTSD. A diminished capacity for emotion regulation is also evident in PTSD samples [65, 66]. In a veteran sample, emotion dysregulation fully mediated the relationship between PTSD severity and impulsive aggression [67]. The FIRST Protocol involving techniques to work on regulating emotions related to aggression, and irritability; both in PTSD/CPTSD symptoms [62]. Emotional regulation is hypothesised to be a cognitive mechanism for the FIRST protocol since it provides veterans with the required skills and cognitions for regulating their emotions, and particularly symptoms of hypervigilance, aggression, irritability, reactivity and dissociation. We therefore hypothesise that improved emotional regulation is a

cognitive mechanism pathway for the FIRST protocol.

Impairments in memory and executive control functions are among the most consistent cognitive deficits in PTSD [68]. A meta-analysis of 60 studies demonstrated that verbal learning and memory, speed of processing, and attention/working memory showed the largest effect sizes [69]. Deficits in declarative memory are most often observed. PTSD literature demonstrated: a) verbal memory impairments (VM), b) disassociation between verbal and visual memory (impaired verbal, intact visual memory), and inconsistencies on either both forms of memory impaired, or both remaining intact [70]. Producing emotionally processed or integrated traumatic memories is likely to be an important mechanism of change for reducing intrusions and re-experiencing of the traumatic event, or from the dissociation that occurs in CPTSD leading to depersonalisation or derealisation, significantly affecting self-concept. Dissociation is a mental process where a person disconnects from their thoughts, feelings, memories or sense of identity. The FIRST protocol achieves that by double disassociation, which requires the client to observe a 'here and now' self (dissociation) observe a 'there and then' self (double dissociation) experiencing the trauma memory. This is then further developed by changing the visualised movie of the experience making it black and white rather than a colour movie. Each of these dissociative steps lessen the impact of the trauma memory on the client, thereby making it easier to process. According to the literature, verbal memory has a greater effect on the traumatic memory [38] [39] . This is achieved through a retelling of a revised version of the trauma memory in the final element of the FIRST protocol, the rescripting element. We therefore hypothesize that the memory mechanisms pathway involves emotionally processed or integrated traumatic memories which reduce PTSD symptoms (intrusions and re-experience of the traumatic event).

Non trauma related autobiographical memory is considered to be negatively affected in PTSD, with evidence of less specificity in autobiographical memories in those presenting with PTSD, [71] therefore we hypothesise that autobiographical memory will improve through the rescripting process in the final step of the FIRST protocol. This stage requires the client to generate a revised version of the trauma event, changing key details by removing the perpetrator or damaging object from the revised version, and, also ensuring that the revised movie has a different ending, with this ending leading to different consequences. The literature suggests that executive function, including attentional processes and processes of storing and manipulation of information of traumatic memories, present major deficits in people experiencing PTSD/CPTSD symptoms [69]. Specifically, working memory performance (WMP), which is an important cognitive function for our ability to store, retrieve and manipulate information related to trauma, plays a key role in explaining and altering symptoms of arousal in people with PTSD [72]. Interventions focusing on alterations/training of retaining and manipulating information related to traumatic memories (WMP) have shown to be effective on reducing post-traumatic stress symptoms [73]. On the other hand, attentional allocation seems to be important in the relationship between the ability to store and manipulate information and PTSD symptoms, with scholars proposing that attentional allocation may serve as the intersectional mechanism connecting working memory to trauma [74]. We therefore hypothesise that alterations in storing, retrieving and manipulations of trauma related memories reduces symptoms of hypervigilance. In addition, the ability to resist interference from trauma related stimuli is negatively impacted in people with PTSD/CPTSD. As examples, Scott et al. (2015) [69] meta-analysis examined a broad range of cognitive domains and found small to medium effect sizes (range, Cohen's $d$ = −0.29 to −0.62) for PTSD as an independent variable, with the largest effects sizes in the domains of verbal learning (Cohen's $d$ = −0.62), information processing speed (Cohen's $d$ = −0.59), and attention/working memory (Cohen's $d$ = −0.50) **[75]**. We therefore hypothesise that alterations on veterans' ability to resist and avoid interference from negative stimuli (attention) is an active ingredient of FIRST in improving symptoms of PTSD/CPTSD in veterans.

### 7.2 Research impact

This research will be the first to test therapies incorporating NLP and cognitive techniques process under robust trial conditions and increase understanding for its mechanistic pathway. It will thereby deliver evidence to the neurocognitive, psychiatric and psychology clinical communities on how these, almost always, brief interventions could be understood and targeted in clinical practice. Understanding mechanisms using well documented science is key to enabling these communities

to be curious about, and develop greater trust in, therapies incorporating NLP techniques and reconsolidation process.

**Table 1. Primary hypotheses.** Testing these will allow us to achieve our primary objective of determining what specific psychological mechanisms explain the FIRST protocol's effectiveness.

| **Hypothesis [H]** | **Mechanism** | **Level and prediction (P=psychological hypothesis; S=symptom hypothesis)** | **Executive function** | **Psychological Assessment Task** | **PTSD Symptoms** |
|---|---|---|---|---|---|
| H1: FIRST improves ability to remember and reproduce emotionally free neutral memories | Emotionally processed or integrated traumatic memories reduce dissociation and PTSD symptoms | **At psychological level (P1)**: The treatment group compared to controls will experience improved trauma memories | Memory | The Trauma Memory Quality Questionnaire (TMQQ) | Dissociation, intrusions and re-experience<br><br>PCL-5<br>Dissociative Experiences Scale- II (DES-II) |
| H2: FIRST improves ability to resist interference from negative stimuli resulting to improved attentional focus and inhibitory control | Alterations in ability to resist interference from distracting stimuli, and therefore effectively move attention away from trauma. | **At psychological level (P2)**: The treatment group compared to controls will experience improved attention focus and inhibitory control | Selective Attention: *Attentional facilitation, interference and avoidance*<br><br>Inhibitory control | Emotional Stroop task | Hypervigilance- and arousal<br><br>PCL-5<br>(DES-II) |
| H3: FIRST improves regulation of emotions in relation to the traumatic event | Improves ability for regulating emotions and PTSD | **At psychological level (P3):** The treatment group compared to the controls will show improved self-regulation | Emotional regulation | Cognitive Emotion Regulation Questionnaire–Short (CERQ-Short form) | Aggression, irritability and reactivity<br><br>PCL-5<br>DES-II |

| | | | | | |
|---|---|---|---|---|---|
| H4: FIRST improves self-appraisal and reduces negative appraisals in relation to self and increases access to specific autobiographical memories | Facilitates improvement in autobiographical memory and alterations on overall value that one places on oneself as a person, the tendency to have a negativistic cognitive/explanatory style and to focus on negative aspects of the self and beliefs about the causes of events in one's life | **At psychological level (P4):** The treatment group, compared to the control will show improved self-appraisal and autobiographical memory which will result in improvements in trauma related appraisals (shame, fear, anger) and non-trauma related outcomes (self-esteem) | Negative cognitions to self | Post-traumatic Cognitions Inventory Scale<br><br>Autobiographical Memory Task (AMT)<br><br>The Self-esteem scale | Guilt, shame, dysfunctional conditions<br><br>PCL-5<br>DES-II |
| H5: FIRST improves executive functioning by improving WM (Working Memory) processes which reduce PTSD symptoms | Alterations in storing, focusing attention on, and manipulating information of traumatic memory. | **At Psychological level (P5):** The treatment group compared to control will show improved storing, encoding and retrieval of traumatic memories | Working Memory | Digit forward & backward task | Arousal Intrusions<br><br>PCL-5<br>DES-II |
| The above reductions will correlate with the level of symptom improvement that patients experience following FIRST. | **E/A*** | **At symptom level (S1):** Changes (between time 1 and time 2) in the measures of intrusive memories, avoidance, self-regulation, negative appraisals, and hypervigilance will predict reductions in PTSD and dissociation symptoms. | Group Covariates of task summaries | PCL-5<br><br>DES-II | N/A* |

*E/A: explained above

# 8 Trial design

A single centre, individually randomised clinical trial to determine the efficacy of FIRST compared to waiting-list control on PTSD symptom severity at 20 weeks. The trial is preceded by a FIRST proof of concept trial and incorporates a mechanistic evaluation.

## 8.1 Study population

Participants are male and female UK-based military veterans who suspect, or know, they have a diagnosis of PTSD and/or CPTSD.

## 8.2 Eligibility criteria

### 8.2.1 Inclusion criteria:

- UK based military veterans from the Royal Navy or Royal Marines, British Army, Royal Air Force;
- Aged ≥18 years;
- Currently living or working in the UK;
- Ability to read and speak English;
- PTSD diagnosis determined by DMS-5 using the Clinician Administered PTSD scale (CAPS-5)
- Experiencing symptoms causing clinically significant distress or impact on social, occupational or other areas of functioning;
- Self-reported history of exposure to one or more traumas;
- Willing and able to provide informed consent;
- Willingness to be randomised to treatment group;
- Willingness for the therapy sessions to be video recorded.
- Access to the Internet.

### 8.2.2 Exclusion criteria:

- Currently receiving psychological treatment for PTSD;
- Currently has a comorbid DSM-5 mental health or personality disorder sufficiently severe as to intrude upon the participant's ability to cooperate with treatment.
- Participants who have had a self-reported suicide attempt within the past month;
- Current dependence on alcohol as determined by an AUDIT cut off of ≥20 [76] or self-report of prescription or illegal substances dependence.
- An existing dissociative disorder as determine by scoring ≥43 on the Dissociative Experiences Scale [77]
- Self-reported medication changes in anti-psychotic and anti-depression medication in the previous four weeks.
- Any other documented reason in which the assessing assistant psychologists, in consultation with their clinical supervisor, determine that treatment for other mental health symptoms takes precedent over their PTSD at the time of assessment.

## 8.3 Participant recruitment strategy for all phases of the project

### 8.3.1 Recruitment campaign

We will use a funded and targeted UK-wide social media campaign which will be supported by existing and establishing new networks though the PPIE group, the veteran charity sector and regimental sectors and veteran research groups. This method and collaboration was successfully used in the feasibility trial.

1) Nativve Health Research (https://www.healthresearch.study) will develop a targeted social media digital advertising campaign. Their algorithms target veterans living in specific UK regions and with specified age, ethnic and gender profiles. The veteran community has a high social media presence and the campaign will use the following platforms: FaceBook, Instagram and X, formally known as Twitter. We expect high levels of organic veteran community traffic "likes" and "shares". The social media campaign will support recruitment

of veterans who have not remained close to their regiments or engaged with local veteran charities. The social media campaign will be developed to ensure it reaches women, older veterans of 70 years and over and ethnic minority veterans. The campaign will be escalated/de-escalated according to study needs each month to support the recruitment targets. The website design will be inclusive. We aim for our randomised population to be a minimum of a) 3% from an ethnic minority, b) 14% women and c) 20% veterans ≥ 70yrs. There will be no upper limits on these recruitment targets.

2) We will advertise our research to women veterans via the Centre for military women's research CMWR: Get involved, take part, or collaborate! (centreformilitarywomensresearch.com) and the female veterans cluster of the Confederation of Service charities (Female Veterans - Cobseo) and via the Female Veterans UK Facebook Group.

3) We will engage with the UK-wide veteran charities that supported recruitment to our feasibility trial and were involved in our dissemination work using traditional and online media announcements, as well as reaching out to new veteran charities and the Regimental Sector to tell them about our study and invite them to support us with recruitment. We will offer online seminars and 1:1 meetings to explain our work and support the establishment and delivery of recruitment pathways as proved successful in the feasibility trial. We will promote awareness of the study using our Institutions' and funders' social media feeds and relevant media outlets. Our PPIE group and experienced members of the research team will identify the charities and Regimental Sectors that we should establish relationships with.

### 8.3.2 Expressions of interest

Through exposure to study information through the channels above, potentially interested participants will access our study website where they will find further details about the study and a link to the participant information sheet. Some potential participants will be supported to engage with the study website by their family, regimental peers or the charity sector although we expect the majority to self-refer. The website will signpost veterans who decide not to take part to veteran organisations and NHS helplines who offer support. Those veterans interested in finding out more about taking part will register their eligibility and interest by submitting their contact details directly to the King's study email inbox via the study website. All potential participants leaving their contact details will be contacted by a named member of the research team via our study email or telephone.

### 8.3.3 Eligibility screening

1) Initial self-reported screening via the website.
2) Following expression of interest, potential participants will be asked to complete the online PCL-5 scale to screen for the severity and breadth of PTSD symptoms [22] and the AUDIT questionnaire [76] to screen for alcohol dependency. If they score >32 on the PCL-5 and <20 on the AUDIT, potential participants will be asked to complete informed consent by a member of the trial management team and they will be invited for an eligibility confirmation assessment via videocall within two weeks.

### 8.3.4 Eligibility confirmation assessment

Once informed consent (see details below) is obtained participants awaiting final eligibility confirmation will be given an appointment within two weeks to undertake the 90-minute eligibility confirmation assessment by an assistant psychologist specifically trained for the trial.

The assessment incorporates a PTSD eligibility confirmation interview using the CAPS5[23], the (ICD-TQ) [25], which will determine the presence of clinically significant PTSD and its subsequent level of complexity and the Dissociative Experiences Scale (DES) [77] to determine whether they have a dissociative disorder which is an exclusion criteria. In addition, a general mental health screening assessment will be completed to identify presence of any mental health exclusion

criteria and determine historical and comorbid challenges including medical, cognitive ability, perceptual disturbances and presence of substance use that could impact their capacity to engage with a course of therapy (i.e therapy-readiness). Those not eligible will be referred back to any referring organisation by the research team, or, if self-referred, supported by a research team member to engage with alternative help from the NHS and/or charity sectors. Participants assessed as eligible to join the study will be randomised into the trial.

### 8.4 Informed consent procedures

Expressions of interest from the social media campaign will be received in the research email inbox. The research team will email the potential participants with the participant information sheet and a Qualtrics link containing the PCL-5 and AUDIT screening questionnaires. Potential participants can complete these forms independently or with the support of the researcher. They will provide consent for us to process this data which will be deleted immediately, along with any personal contact details, if they are ineligible or decide they no longer wish to explore taking part in the trial. If they score >32 on the PCL-5 and <20 on the AUDIT, a member of the research team will contact the potential participant by phone or email to discuss the study, answer questions and review the informed consent form. Potential participants will have until the close of phase 1 proof-of concept, or phase 2 trial, recruitment periods to consider whether to take part. Once they decide to proceed, informed consent will be undertaken via Qualtrics, either independently or with the support of a researcher. The signed consent form will be co-signed by the researcher using PDF editing software and returned to the participant via email. The electronic consent form will be stored on a secure, password protected server. No hard copies will be kept.

Those veterans who score <33 on the PCL-5 or >20 on the AUDIT or those that are eligible but decline to take part will be signposted to available support services.

### 8.5 Assistant Psychologist training and supervision

An experienced clinical supervisor (investigator Josh Kreft) will train and supervise the assistant psychologists completing the semi-structured assessments for the study. Following recruitment, the assistant psychologists will be required to complete self-directed reading on the CAPS-5, DES-11 and ITQ in order to orientate to the assessment tools. Following this they will complete a six-hour training session with the clinical supervisor to train them in the administration of the general mental health screening and CAPS-5 semi structured interview. Following this training the clinical supervisor will observe each assistant psychologist undertake two separate assessments for the supervisor to review for quality assurance purposes. One session will take place during the first four weeks of the trial starting and the second within three months. Following this the AP's will receive regular bi-monthly group supervision with the clinical supervisor to review completed participant assessments that require further review from a senior clinician regarding suitability and ability to engage.

**Table 2: Assistant psychologist training and supervision**

| **Mental Health Screening and Assessment Training** | |
|---|---|
| **1** | Self-directed learning – 2 hours. |
| **2** | Live online teaching face to face by Josh Kreft – 6 hours |
| **3** | Successfully undertake – under observation from Kreft – eligibility confirmation assessments with two potential trial participants, JK will review to ensure standard of the CAPS-5 is adhered to. (1x 90min session within 4 weeks of completion of the training, then 1x 90min session within 3 months of completion of training) per Assistant Psychologist – 3 hrs |

| Clinical Supervision | |
|---|---|
| **4** | Clinical supervision – 1.5 hour group supervision bi-weekly over course of trial |

### 8.6 Planned interventions and delivery

The experimental therapy, FIRST, uses non-propriety, copyright free, techniques with the intellectual property shared between Lisa de Rijk and King's College London. All participants will be randomly allocated to receive FIRST within three weeks of randomisation or to a waiting list group who will receive FIRST 20 weeks following randomisation.

### 8.7 Experimental intervention

FIRST is a brief intervention with minimal and non-traumatising exposure to the original stimulus. It is delivered in 3 to 4 x 90-120 minute sessions by a FIRST therapist via videocall. FIRST rewrites the emotional elements of the memory. FIRST therapy will be delivered over a minimum of three days and a maximum of four weeks. The two factors determining this are a) there must be one sleep cycle between each therapy session and b) scheduling of therapy sessions for the participant and the therapist. The evidence to date indicates that therapy should be completed within four weeks. The FIRST protocol incorporates 18 steps in five stages (table 3). Participants will be asked at all data collection timepoints if they have undertaken any additional therapy for other mental health symptoms such as mood or anxiety, as well as any additional therapy for PTSD.

**Table 3. The FIRST Protocol and therapeutic Stop/Go points**

| Stage | Clinical technique | Theory/evidence for the technique |
|---|---|---|
| Pre- randomisation assessment by DES [77] | The potential participant is assessed to determine their ability to manage their own association and dissociation processes for suitability of the FIRST protocol. | Participants scoring <31 on the DES-11 proceed as per therapy protocol. Go point 1.<br>Participants scoring between 32-42 (referred to as High DES-11 in following text) proceed with therapist treating them as if the client has complex PTSD and an active dissociation mechanism and modifies therapeutic protocol. GO point 1.<br>Participants with DES-11 score ≥43 should have been excluded prior to randomisation. STOP point 1. |
| i). Priming process | Prior to commencing work with a trauma memory, the client is primed to the process by completing a full run through of the key elements of the protocol on a neutral memory experience. | Associational learning provides the opportunity during the priming process to strengthen prefrontal cortex synapses required for memory reconsolidation and alteration in decision making processes [66]. NLP trauma therapy techniques use priming processes before the client engages with the trauma story [21, 29, 78].<br>If the client has a high DES-11 score at assessment, the protocol follows a revised 'neutral activity double dissociation' visual format at this point. If the client can manage this they proceed into the protocol treatment. – GO point 2.<br>If the client cannot follow the revised visual format |

| | | |
|---|---|---|
| | | on a neutral activity at this point, they do not proceed. STOP point 2. (See Appendix 1 – safety protocol for how we  See safety protocol for how we manage trial withdrawal for these participants. ) |
| ii). Desensitisation process through dissociation | A series of black and white movie repetitions of the trauma event are observed from a twice or doubly dissociated position | The NLP trauma therapy techniques utilise modified variations of black and white movie formats to facilitate dissociation from trauma memory and response [21, 29, 36]. Fear cascade mechanism and the neurobiology of dissociation enables the management of hyperarousal, flashbacks, any derealisation process including dissociation in response to trauma, splitting or collapse mechanisms before the client is required to access an associated memory structure [79, 80]. |
| iii). Undoing of trauma memory through reversed imagery | A fast associated, re-experiencing the trauma memory in their own body, as a reversed or run backwards imagery of a trauma memory | Individuals with PTSD have a maladaptive response to processing emotions and are stuck in a trauma response that continues to activate a hyperarousal response when certain triggers occur, effectively resulting in the individual continually reliving the trauma experience. By using a fast associated reversed imagery of a trauma memory found in NLP Trauma Therapies [21, 28, 29, 36] associational learning and adaptive responses are altered and afforded the potential for reconsolidation in the final stage of the processes [81, 82]. |
| iv) Reconsolidation | A new story to the memory is developed which rewrites the emotional elements of the original memory | Rewriting the emotional elements of the memory takes advantage of the hypothesised phenomenon of reconsolidation [32, 83-85]. Reconsolidation describes the reactivation of long term, otherwise permanent memories, by their evocation in certain contexts.  When a memory is reactivated, it labilises, that is, it becomes subject to change. By changing the circumstances surrounding the memory and if the new circumstance provides evidence that a threat of negative emotional stimulus is no longer relevant, the strength of the affective charge may decrease. One NLP Trauma therapy which shares some characteristics with FIRST, RTM, is theorised to use the mechanism of reconsolidation to enable the rewriting of trauma memories [27, 31]. |

### 8.8 FIRST therapy clinical setting

Our therapy delivery and clinical governance partner and collaborator is Inspire; a mental health charity located in Northern Ireland (https://www.inspirewellbeing.org/) who delivered all therapies remotely in the feasibility trial. Inspire therapists are experienced in working remotely with cross-UK

and Republic of Ireland military veterans since online mental health assessment and therapy became mainstream therapeutic provision during the COVID-19 pandemic. In addition, participants in the feasibility trial reported Inspire therapists were knowledgeable, understanding and well-trained [25]. For an efficacy trial this third sector organisation offers a more *ideal setting* for the following reasons: a) the flow of participants through the trial is controllable because there are many fewer competing interests than within the NHS; b) Inspire, due to their Northern Ireland location, have considerable expertise in working with military veterans and other populations with occupationally-related PTSD; c) they have robust clinical governance procedures which are adaptable to being supplemented with FIRST therapy-specific clinical supervision.

### 8.9 Therapist recruitment and eligibility assessment

The trial requires twelve therapists to competently deliver FIRST as per the intervention delivery timeline. We recognise that twelve therapists introduces variability, of therapist effect for example [86] [87] but this is offset with the advantages of twelve providing greater external validity. Existing Inspire therapists who achieved competence while delivering therapy in the feasibility trial will be invited to apply to join the trial. Additionally, we will recruit 8-10 independently employed therapists who meet the following criteria:

- Hold full clinical registration with either the British Association for Counselling and Psychotherapy (BACP), the National Counselling and Psychotherapy Society, Accredited Professional Registrant (NCPS Acc.) the British Association of Behavioural and Cognitive Psychotherapy (BABCP), the United Kingdom Council of Psychotherapy (UKCP), the Irish Council for Psychotherapy (ICP), or equivalent.
- Candidates will be considered if they have completed their core training hours under a UKCP, ICP or BABCP approved training organisation and have completed a minimum of 250 client contact hours under clinical supervision.
- Practitioner Clinical/Counselling Psychologists must be registered with the Health Care Professions Council (HCPC).
- Trained in RTM, NLPt Trauma Therapy or Rewind technique.
- Current Professional Indemnity Insurance to £2.5 million.
- Clinical supervision with a BACP/UKCP/ICP/BABCP/HCPC accredited supervisor.
- Access NI, Garda vetting or mainland UK DBS equivalent clearance.
- Attended certified Safeguarding, Child Protection and Adults at Risk or in Need of Protection minimum level – 2 training within the last three years.
- Work to the third sector delivery partners Risk Assessment, Management and Escalation Guidelines with adherence to regional Child Protection and Vulnerable Adults in need of protection policies, procedures and good practice guidance.
- Comply fully with the standards and key performance indicators set out in Inspire's associate counsellor agreement.
- Able to commit to the time required to complete the trial.

Once eligibility is determined they will be onboarded into Inspire as Associate Therapists. Inspire onboarding will comprise:

- Access NI or DBS clearance
- Induction into Inspire's operation and clinical policies and procedures
- Induction to Inspire's information management system
- Receipt of relevant documentary evidence of accreditation, certified child and adult safeguarding training, supervisor's report and professional indemnity insurance of £2.5 million.

### 8.10 Training and fidelity assessment of the delivery of FIRST protocol

Recruited therapists will participate in an additional seven hours, over a single day, of online training to orientate them to, and give opportunity to practice, the specific elements of the FIRST protocol which differ from previous reconsolidation protocols they have delivered clinically.

**Table 4. Programme – one day update for prior trained therapists**

| | |
|---|---|
| 09.00 | Introduction |
| 09.10 | Rationale for FIRST protocol |
| 09.20 | Simple PTSD |
| 09.25 | Complex PTSD |
| 09.35 | FIRST protocol steps |
| 09.45 | DES-11 assessment |
| 10.00 | Complex PTSD neutral activity process |
| 10.30 | BREAK |
| 10.45 | Complex PTSD video demonstration |
| 12.30 | BREAK |
| 13.00 | Protocol exercise in pairs x 2 |
| 15.00 | BREAK |
| 15.15 | Variations to submodalities |
| 15.45 | Protocol principles |
| 16.00 | Research trial – Annmarie Grealish |
| 17.00 | CLOSE |

Following the one-day upskilling training, therapists will practice their skills on two work colleagues or friends or private clients. These sessions will be recorded and assessed for competency by an independent assessor. Following confirmation of FIRST delivery competence, therapists will participate in 14 hours of FIRST specific online clinical supervision delivered by the FIRST trainer in groups and individually via video call to ensure their continuing fidelity to the protocol.

### 8.10.1 Assessment of intervention fidelity

Because FIRST therapy takes place via a video call, and with participant informed consent (see below), each therapy session will be recorded using the online recording facilities within each video-conferencing interface. Once the session is completed the recording will be encrypted, password protected and saved to a secure KCL server. FIRST therapy is protocolised and is based on the principle that rapid dissociation from any hyperarousal state is key. It is very difficult to calibrate this on voice alone, particularly as the arousal response may occur before the client gets to the point of speaking. Therefore, to assess protocol fidelity, video-recordings of *10% (n=21)* therapy sessions of the intervention received by participants will be randomly selected for fidelity checking by a FIRST therapist supervisor who provides independent expertise in reconsolidation protocols. Every three months client therapy sessions will be randomly selected by excel computer-generated random order number for fidelity assessment by this independent expert. Once assessment is complete for that *period*, therapy video recordings will be permanently deleted. The procedure will be repeated every three months in which FIRST is delivered. An adapted version of the Strengths Model Fidelity Scale [88] will be used to assess treatment fidelity. This measure aligns with FIRST's incorporation of strengths-based protocolised components therapy and a focus on keeping the client in a resourceful state. Therapists are required to adhere to the main constructs in strengths-based therapy while being sufficiently flexible to meet clients' needs.

### 8.10.2 Comparison intervention

Participants randomised to the waiting list control (WL) group can continue with any ongoing care or newly engage with usual care pathways available in NHS veterans' services and charities for non-PTSD mental health concerns. Participants will be offered FIRST therapy following the completion of data collection at 20 weeks post randomisation. They will be informed of the appointment date/time for FIRST therapy commencement at the point of randomisation. Safety data is collected at six and 12 weeks and our well-performing feasibility study safety protocol will ensure that any escalation of symptoms in waiting list participants will be detected and recorded as

an adverse event (Appendix 1).

# 9 Phase 1: Proof of concept study

## 9.1 Research question

Does FIRST have similar efficacy signals as RTM at 12 weeks with the same therapy dose?

## 9.2 Study design

This concords in size with the RTM arm of the feasibility trial and planned procedures for the main trial in phase 2 as described above. Outcome data collected at 12 weeks is appropriate because the mean PCL-5 score in the RTM group showed little difference between 12 weeks (35 (SD 17)) and 20 weeks (38 (SD 18)). The research procedures, except for randomisation and the mechanisms data collection procedures, are as for the main trial. Participants, setting, recruitment, informed consent and intervention details are presented in previous sections  Below are additional procedures only for the POC study.

## 9.3 Procedures

The 30 participants will be recruited in three months with completion of six-week safety data and 12-week follow up data on PTSD symptoms and depression symptoms.  Participants will complete the mechanisms task battery proposed for the trial at baseline and 12 weeks (see Appendix 2).

## 9.4 Progression criteria

We will consider POC on the basis of the progression criteria detailed in table 5. These incorporate criteria and procedures to identify early signals that FIRST may/may not be working, two stop/go points are in the protocol (table 4) and observation of the PCL-5 MCID of 10 points (see analysis below). In the feasibility trial, 4 of 35 participants were deemed unsuitable by the therapist for the RTM protocol. Inability to stay in a neutral state and avoid emotional trauma flooding (becoming overwhelmed by their emotions) when sympathetic arousal was observed were the main reasons. Emotional trauma memory flooding is a contraindication for both RTM and FIRST protocols as ability to cognitively dissociate from the trauma experience is essential to the protocol delivery. Eligibility criteria will assess for this using the DES-11 [77] (see eligibility criteria and table 4).

## 9.5 Analysis

The statistical analysis plan (SAP) outlining all the analyses of the POC data will be developed during the trial set up period and before completion of the POC and will be signed off before any data analysis commences. In summary, the mean change from baseline to 12 weeks on PCL-5 scores of the FIRST POC cohort will be compared to the RTM arm data collected during the PETT feasibility study. We will estimate the mean and CI of the change in PCL-5 between baseline and 12 weeks, for the two cohorts. We will then compare them using both the mean change from baseline and the CIs of the mean change. We expect the CIs to be of similar width and to largely overlap if the treatment effect signal in the POC is similar to the treatment effect signal in the feasibility.  We will compare the total number of therapy minutes of both RTM and FIRST therapy sessions completed to achieve the effect signal.

**Table 5. POC study progression criteria using traffic light system (green represents 100% concordance with planned targets)**

| Progression criteria | No (%) of (potential) participants | Rationale |
|---|---|---|
| Eligible to proceed to | 30 (100%) | In the feasibility trial 4/35 (11%) of participants |

| | | |
|---|---|---|
| receive FIRST therapy | ≥27/30 (11%)<br><27/30 (>11%) | had contraindications to receiving RTM, identified post-randomisation at therapy commencement. We will evaluate our new general mental health eligibility assessment processes (pre-randomisation) to determine participants are FIRST-therapy ready. |
| Therapy toleration | ≥25 (83%)<br>15-24 (50-82%)<br><15 (50%) | PTSD does not resolve itself without treatment so between and 15 and 30 participants (50% or over) tolerating therapy offers significant potential treatment gain. |
| Efficacy signal – proportion of participants reaching the 10-point MCID reduction at 12 weeks | ≥14 (45%)<br>9 -13 (30-44%)<br><9 (30%) | Our feasibility trial found 48.5% of RTM participants met the 10-point MCID PCL4 reduction at 20 weeks. PTSD does not resolve itself without treatment so with the potential of an efficacious brief therapy an equivalent efficacy signal in at least 30 participants (50%) offers significant potential treatment gain. |

## 10 Phase 2: Trial

The randomised controlled trial will run for 19 months with a five-month internal pilot. Data collection will continue up to the 20-week primary outcome timepoint for both arms of the study with 52-week maintenance of effect data collected for the Intervention arm only (see Appendix 2).

### 10.1 Baseline data collection

At baseline, consenting and eligible participants will complete primary, secondary and mechanisms outcomes, demographic and medical history questionnaires via Qualtrics online survey software. Socio-demographic and medical history variables collected are age, sex, ethnicity, occupational and co-habitation status, type and duration of military service and GP contact details. Related to their PTSD history we will collect data on PTSD symptoms, previous confirmed PTSD diagnoses, number of traumas and previous treatment attempts and current and previous three months' self-report pharmacotherapy and psychological therapies. Cognitive assessment data will be collected via PsychoPy software.

### 10.2 Data collection procedures (see Appendix 2)

*Qualtrics survey software* will be emailed to the participant for self-completion. They will also be offered support with completion from a researcher, if preferred.

*PsychoPy experimental software* will be used to build the cognitive task experiments with a web link to the experiment emailed to participants for self-completion. The PsychoPy team will provide support in building the experiment and will advise on experimental blocks, tasks and settings. The experiment will begin with information and instructions to the participants on how to complete the tasks. Each task should be completed without any interruptions. Participants will be given the option for a researcher to be online with them while completing the tasks. PsychoPy is compatible with all various servers and can be easily accessed via the study's URL.

These PROMS and mechanisms battery are extensive and present a considerable research burden. We achieved a 75% data completion rates [25] of across all outcomes at 20 weeks by developing and delivering empathic, compassionate and responsive relationships with participants. We will need to work harder to deliver this responsiveness to participants because of the added burden of the mechanisms battery which we will have evaluated in the POC study. Our PPI group

have signposted us to ways to achieve this e.g ongoing positive social media messages from participants will be important for exemplifying our trustworthiness to the veteran community and for keeping people engaged. PPI support will continue to inform our engagement procedures.

### 10.3 Participant compensation

Participants will receive a £15 high street voucher at six-week, 12-week, 20-week and 52-week outcome return, £60 in total.

### 10.4 Withdrawal from the study

Participants may withdraw from the study at any stage without providing any explanation and this will be communicated to them on the participant information sheet and verbally by both the research team and their therapist. If they withdraw before informed consent all data (including personal data) will be deleted. If withdrawal takes place after informed consent participants may request withdrawal of their data up until the point at which the study database is locked for analysis. This will be made clear in the participant information sheet and the informed consent form.

### 10.5 Randomisation and stratification

King's College London Clinical Trials Unit (KCTU) will provide a computer randomisation service. Stratification will be undertaken on diagnosis of PTSD or CPTSD, age and sex. Randomisation will take place after the eligibility confirmation assessment and once baseline data has been completed. Participants will be randomised to the intervention arm where they will receive therapy immediately or to the waiting list control.

Only three members of the research team will be unmasked: the lead clinical provider, the safety monitoring researcher and the trial statistician (the senior statistician will remain masked). All those entering data will be masked to treatment group. For participants randomised to the intervention group, therapy will commence within three weeks. If participant holidays are arranged, randomisation will be delayed ensuring this timeline can be maintained.

### 10.6 Proposed sample size

To detect a mean between group difference of 10-point drop in PCL-5 score (MCID) [54, 57] at 20 weeks, with a standard deviation of 20, taken from our feasibility trial [25] and 90% power (5% significant level), 172 in total (86 patients per group) are required. To allow for a loss to follow up of 20% at 20 weeks. The proposed 20% loss to follow up rate is informed by a review comparing TF-CBT with EMDR, research and treatment attrition ranged from 8–58% with a mean of 29% [17]. However, our feasibility loss to follow up was 20% so we will recruit 215 participants, over 19 months (12 patients per month). We will monitor recruitment to these goals in the internal pilot.

### 10.7 Internal pilot

The internal pilot will monitor recruitment, randomisation, retention in research to 12 weeks and safety of those in the WL group whose symptoms may escalate while awaiting therapy. Recruitment targets and progression criteria for the internal pilot are in table 4. Progression targets are based on an 70% retention to 12 weeks.

**Table 6: Internal pilot recruitment targets and progression criteria using traffic light system (green represents 100% concordance with planned targets)**

| Criteria and targets | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Total |
|---|---|---|---|---|---|---|
| Expressions of interest (EOI) through social media campaign no, (% of green target) | 91 (100%) | 118 (100%) | 136 (100%) | 136 (100%) | 136 (100%) | 618 (100%) |
| | 64 | 83 | 95 | 95 | 95 | 433 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | (70%) | (70%) | (70%) | (70%) | (70%) | (70%) |
| | <64 | <83 | <95 | <95 | <95 | <433 |
| Assessed for eligibility min 24% of EOI | 23 | 30 | 34 | 34 | 34 | 155 |
| | 16 | 21 | 24 | 24 | 24 | 109 |
| | <16 | <21 | <24 | <24 | <24 | <109 |
| Recruited (consented) (min 10% of EOI) | 10 | 12 | 14 | 14 | 14 | 64 |
| | 7 | 8 | 10 | 10 | 10 | 45 |
| | <7 | <8 | <10 | <10 | <10 | <45 |
| 33% of veterans recruited, who are any of:<br>female sex,<br>over 70yrs,<br>ethnic minority | 2 | 4 | 4 | 5 | 5 | 20 |
| | 1 | 1 | 2 | 2 | 3 | 9 |
| | <1 | <1 | <2 | <2 | <3 | <9 |
| Randomisation targets (number of people) | 10 | 11 | 13 | 13 | 13 | 60 |
| | 4 | 8 | 10 | 10 | 10 | 42 |
| | <4 | <8 | <10 | <10 | <10 | <42 |
| Completeness of primary outcome data: 70-100% of the total recruited population providing 12-week data | | | | ≥80% of 34= 27 | ≥80% of 47 = 38 | ≥80% of 60 = 48 |
| | | | | 70 - 79% of 22 = 15-17 | 70 - 79% of 32 = 22-25 | 70 - 79% of 42 = 29-33 |
| | | | | <15 (<70%) | <22 (<70%) | <42 (<70%) |

### 10.8 Trial outcome measures

#### 10.8.1 Trial primary outcome

The post-traumatic stress disorder checklist for DSM-5 (PCL-5) [54, 57, 89] PTSD symptom severity. It is a 20-item self-report measure that assesses the 20 *DSM-5* symptoms of PTSD taking 5-10 minutes to complete. Symptom severity score (range - 0-80) is obtained by summing the scores for each of the 20 items. A PCL-5 cut-off score of >32 indicates likely PTSD. A 5-10 point change represents reliable change and a ≥10point change represents the minimal clinically significant difference (MCID) with the scale having high internal consistency in measuring DSM–5 PTSD symptoms [90].

#### 10.8.2 Trial secondary outcomes

Proposed health and outcomes PROMS demonstrated mean improvements in their MCID during

the feasibility trial in experimental therapy participants. Additionally, we examine therapeutic alliance to understand therapist effect alongside FIRST therapy effects. Therapeutic alliance is among the best predictors of treatment success so we will assess this using the Agnew Relationship Measure – 5 (ARM-5) [37]. This also helps clinicians identify risk of dropout as well as track any ruptures/repairs in the alliance.

*Work and Social Adjustment Scale (WSAS)* assesses impaired functioning [91]. The Work and Social Adjustment Scale (WSAS) is a 5-item scale to assess the impact of the person's mental health on work, home, social and private leisure activities and interpersonal relationships. It has a 9-point assessment scale ranging from *Not at all* to *Very severely.* With internal scale consistency ranging from 0.7 to 0.9 and test-retest of 0.7 it is a valid and reliable scale for assessing impaired functioning in mental ill health [91]. Feasibility outcomes indicated a slightly greater effect signal for reconsolidation protocol (-4.62 (9.16)) compared to TF-CBT (-3.06 (8.23)).

*The Patient Health Questionnaire (PHQ)* assesses depression [92] in a 9-item self-administered diagnostic instrument for depression [27]. It scores each of the 9 mood-related DSM-IV criteria as "0" (not at all) to "3" (nearly every day) [93]. Scores represent: 0-5 = mild, 6-10 = moderate, 11-15 = moderately severe, and 16-20 = severe depression. It is widely used to assess mood in the UK NHS. Feasibility outcomes indicated mean participant scores in both arms achieved the MCID [28] of -1.7 (experimental therapy -2.73 (6.80); TF-CBT -3.07 (6.13)). The PHQ9 is a proposed safety outcome.

*The EQ5D-5L* records participants' self-rated health EQ5D-5L [94] is a two-page questionnaire with page 1 consisting of the EQ-5D descriptive system and page 2 the EQ visual analogue scale (EQ VAS). EQ5D-5L comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ VAS records self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. Feasibility outcomes revealed that the experimental therapy had an effect signal on self-rated health status.

*The Self-esteem scale* assess participants' self-rated self-esteem [95] comprising 10-items measuring both positive and negative feelings about the self. All items are answered using a 4-point Likert scale format ranging from strongly agree to strongly disagree. Scores between 15 and 25 are within normal range, where scores below 15 suggest low self-esteem [29]. The self-esteem scale is included due to the qualitative findings of our feasibility trial revealing improved self-esteem following experimental treatment.

*Agnew Relationship Measure – 5 – ARM-5* [37]. The ARM-5 assesses three dimensions of alliance known to be important for treatment efficacy; Bond (1 item), Partnership (2 items) and Confidence in therapy (2 items). The ARM-5 offers scores between 5-35 indicating an overall level of therapeutic alliance. Total scores, as opposed to subscales scores for bond, partnership and confidence, offers greatest reliability.

### 10.9 Mechanisms study outcomes

The Emotional Stroop task is the mechanisms study primary outcome due to evidence on the neural interaction between emotions and cognitive control (attention processes, working memory and reaction conflict or inhibition) [96].

*1*) *Attentional bias*: a) The emotional Stroop task will be used to assess attentiona bias. The stimuli will use coloured words (red, blue, green, or yellow) shown one at a time in the centre of a computer screen, using all capital letters, on a black background. Colours will not repeat on consecutive words and will equally used throughout all trials. Three types of word stimuli will be used: a) combat-related words, b) negative words, and c) neutral words. The combat-related threat list is to be personally-relevant to combat veterans and is comprised of words related to things encountered in a warzone (e.g., bomb, seize), negative list contains words that were negative in valence, but not related to combat (e.g., tax, witch). The neutral list contains words that are non-

threatening (e.g., self, flour). Word lists will be adopted from the Ashley et al's (2013) study and verified by the study's PPI group [97]. The Affective Norms for English Words (ANEW) will be used for identifying additional words if needed. The ANEW is being developed to provide a set of normative emotional ratings for a large number of words in the English language [98]. Each 30-word list will be presented three times, resulting in 270 total trials (90 neutral, 90 negative, 90 combat related) separated into nine experimental blocks. A blocked design will be selected because, as previous research noted, blocked designs are associated with more robust emotional stroop responses [99]. Participants will be masked to the existence of different word lists per block. We will randomise word order within each list across presentation blocks. Within each emotional stroop trial, participants will first viewed a fixation cross for 1 s, then will view a list item (e.g. 'bomb') for 2 s. Items will be presented in red, blue, or green font, and item colour will be randomly assigned [99]. Individual reaction times of more than two SDs from a participant's mean will be excluded from further analysis [100]. Slower mean reaction times on threatening relative to neutral words ('Stroop interference') is interpreted as evidence of an attentional bias [101]. The emotional stroop task has been widely used to assess attentional bias in veterans with PTSD [102].

2) *Memory*: a) Trauma Memory Quality Questionnaire (TMQQ) is a 11-items tool assessing the quality of traumatic memories than frequence of memories. The items refer to visual quality, a variety of non-visual sensory qualities (e.g. auditory, olfactory, proprioceptive sensations), temporal context, and the extent to which the memory is in a verbally accessible format. Participants can respond to each item by indicating "Disagree a lot", "Disagree a bit", "Agree a bit", or "Agree a lot", scored 1, 2, 3 or 4 respectively, and summed to yield a total score [103]. Some items are reverse scored so that higher scores represent memories associated with greater post-traumatic stress and worse quality of traumatic memories. The scale has shown good internal consistency (Cronbach's alpha of 0.82 in an emergency department sample) and has established construct validity, showing positive correlations with PTSD symptomatology and with re-experiencing symptoms in young adults [104] [105]; b) Autobiographical memory task (AMT): will be administered to measure memory specificity. Participants will be provided with instructions and asked to provide a specific memory to two example words. They will then be asked to generate a memory to fifteen cue words (five positive; five negative; five neutral). Consistent with previous research [106], their responses will be coded as specific (i.e., a single event that occurred at a certain time and place, lasting less than 24 h e.g. "Lunch at a cafe with friends last week'), extended period of time (e.g., 'my time at school'), categoric (summarising repeated events, e.g., 'every time I go for a walk') or a semantic associate (information from general semantic knowledge e.g., 'I don't like eating eggs'). If the response is a repetition, an event from the day of testing, or no response is given then it will be classed as an omission. The score will be the total number of specific memories generated to the cue words (with a total of 15). The AMT is the most widely used measure of memory specificity and has demonstrated adequate psychometric properties [107]. There has been some research using the AMT with military personnel [102, 108].

3) *Working memory*: Digit forward & backward task will be used to assess working memory. A session of digit forward task (8 trials) and a session of digit backward task (8 trials) will be completed sequentially. Each trial starts from a string of six digits (randomly generated by the computer) that will be presented in sequence on the screen, one digit per second. Then a blank screen will be displayed for 10 s, during which the participants will be instructed to look at the screen and covertly rehearse the given digits continuously. After this retention interval, a number will be displayed on the screen. The participants will be instructed to recall the digits either in the same order (forward task) or reverse order (backward task) as they were presented, by clicking the on-screen number buttons. All participants will finish the forward or backward recall within 10 s. At last, an inter-trial interval of 10 s will be given before the next trial. A 10-s inter-trial interval would be sufficient for the hemodynamic signal to recover to the baseline level, while maintaining participants' patience on the task [109]. For both digit forward and backward tasks, the task difficulty depended on the length of digit string [110]. We will select a six-digit tasks because they

are at an intermediate level and can be completed without extreme difficulty according to a study with control and PTSD veterans [111]. The participants will always be instructed to complete the digit forward task first. Because the digit forward task was easier than the digit backward task, this sequence allowed the participants to adapt to the following more difficult task session. The accuracy of each participant's performance in each type of task will be measured by the percentage of trials of correct retrieval relative to the total number of trials (=8) in each session [111]. The task has been used to assess working memory in veterans with PTSD [111]. Before each formal measurement session starts, all participants will be trained to practice a few trials.

4) *Self-regulation*: Cognitive Emotion Regulation Questionnaire– Short (CERQ-Short) is an 18-item tool that measures cognitive emotion regulation strategies in response to the experience of threatening or stressful life event on a five-point scale from 1 (never) to 5 (always) in terms of 9 subscale [112]: Self-blame; other Blame; Focus on thought rumination; Catastrophising; Putting into perspective; Positive refocusing; Positive reappraisal; Acceptance; and Refocus on planning. The minimum scores in each subscale are 6 and 10, respectively, and a higher score indicates more use of that cognitive strategy. Cognitive emotion regulation strategies fall into two general categories: adaptive and maladaptive strategies. The CERQ has been shown to have good factorial validity, good discriminate properties and good construct validity [112].

5) *Disassociation:* The Dissociative Experiences Scale II (DES-II) is a 28-item tool that measures degrees of dissociation in response to traumatic life experiences. Specific symptoms of derealisation, depersonalisation, amnesia and absorption, common factors in complex PTSD, provide the basis for the scale questions. Each question provides a description of an experience and asks the participant the percentage times they experience this in their everyday life, from never (0%) to always (100%). The average of all answers provides the DES-11 score, with a maximum score of 100%. High levels of dissociation are a score of 30 or more, with a score range of 32-42 suggestive of PTSD. The DES-II has been shown to have good convergent and predictive validity [77, 113].

6) *Negative cognitions*: Post-traumatic Cognition Inventory Scale (PCI-9) consists of nine items and three subscales: negative cognitions about the self, negative cognitions about the world, and self-blame. Questions are rated using a 7-point Likert-type scale ranging from 1 (totally disagree) to 7 (totally agree). PTCI-9 total scores are calculated by taking the mean of the PTCI nine items. Subscale scores are determined by summing each item in the subscale to calculate a raw subscale score and then dividing by the number of items in the subscale, which results in a mean subscale score [114]. The PTCI-9 showed strong internal consistencies (Cronbach's α= .80-.87) and strong correlations with the PTCI in veterans (rs = .90-.96) [114, 115].

### 10.10 Assessment and follow-up

#### 10.10.1 Trial and mechanisms person reported outcomes measures (PROMS)

The primary outcome of PTSD symptoms is assessed at 20 weeks (T4) (table 5). Secondary outcomes are assessed at baseline (T1), and at the final endpoint of 20 weeks (T4). The FIRST experimental arm only will continue to 52-week follow up (T5) of all clinical outcomes to determine maintenance of effect. The mechanisms battery will be assessed at baseline (T1) and 12 weeks (T3). Table 5 presents the PROMS and mechanisms battery.

**Table 7. PROMS (P) and mechanisms battery (M)**

| Survey/task & purpose<br>N=215 | Time 1<br>(baseline) | Before each therapy session | End of final session | Time 2<br>(6-wk) | Time 3<br>(12-wk) | Time 4<br>(20-wk) | Time 5<br>(52-wk) |
|---|---|---|---|---|---|---|---|
| PTSD symptoms (PCL-5): a) Primary trial outcome and b) therapist safety monitoring c) Trial safety outcome (P) | X | X | | X | X | X | X |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Work and Social Adjustment Scale (WSAS) Secondary outcome (P) | X | | | | | X | X |
| The Patient Health Questionnaire (PHQ9) Trial safety outcome (P) | X | | | X | X | X | X |
| Health status EQ5D-5L Secondary outcome (P) | X | | | | | X | X |
| The Self-esteem scale Secondary outcome (P) | X | | | | X | X | X |
| Emotional Stroop Task Mechanisms primary outcome (M) | X | | | | X | | |
| Autobiographic Memory Task (AMT) (M) | X | | | | X | | |
| Working Memory Digit forward & backward task (M) | X | | | | X | | |
| Trauma Memories Quality Questionnaire (TMQQ) (M) | X | | | | X | | |
| Cognitive Emotion Regulation Questionnaire– Short (CERQ-Short) (M) | X | | | | X | | |
| Post-traumatic Cognitions Inventory Scale (PTCI-9) (M) | X | | | | X | | |
| Dissociative Experiences Scale- II (DES-II) (M) | X | | | | X | | |
| Agnew Relationship Measure – 5 – (ARM-5) (P) | | | X | | | | |

## 11 Data analysis

i) Internal pilot feasibility outcomes will be assessed against the expressions of interest, recruitment, randomisation and retention feasibility outcomes presented in table 4. The recruitment targets will be adjusted as necessary following month 12 and the social media recruitment campaign dialled up or down as appropriate to reach full randomisation as per the project plan.

ii) The primary outcome analysis will estimate the difference in PCL-5 at 20 weeks between the two treatment groups (FIRST vs. WL) by using a linear mixed model to account for the repeated measures of PCL-5 in time. The model will include the measurements of baseline PCL-5, treatment indicator, centre indicator and group indicator as covariates. The linear mixed model of PCL-5 (outcome) will include the repeated measures of PCL-5 at baseline, time 2 (6 weeks), time 3 (12 weeks) and time 4 (20 weeks), with time as fixed effect and patients as random effect, the treatment indicator, and will be adjusted by the stratification factors, and any other prespecified factor. We will also include a time by treatment interaction term. As a secondary analysis of the primary endpoint, we will estimate the difference between the groups in the proportion of patients that reach the MCID using a chi-square test. A statistical analysis plan (SAP) outlining analyses of primary and all secondary outcomes will be written and signed off before any look at the data.

Criteria for measuring compliance to the interventions will be pre-specified. In order to account for therapist effect in the analysis of the primary outcome, PCL-5, we will use a linear mixed model, to account for the repeated measures of PCL-5 in time and that will include “therapist” as a factor. Because of the number of therapists (12 therapists), “therapist” will be included in the model as a fixed effect. Hence the linear mixed model of PCL-5 (outcome) will include the repeated measures of PCL-5 (at baseline, time 2 (6 weeks), time 3 (12 weeks) and time 4 (20 weeks)), with time as

fixed effect, patients as random effect, the treatment indicator, therapist as fixed effect, the other stratification factors, and any other prespecified factor. We will also include a time by treatment interaction term. Similarly, therapist effect will also be accounted for in the analysis of WSAS, PHQ-9, EQ5D-5L and the Self-esteem scale.

The SAP will also outline the Mediation analysis to test any predefined mediator. [116] Analyses will be conducted using the STATA 17 software. iii) The Mechanisms study primary outcome analysis will estimate the difference in Emotional Stroop task reaction time at 12 weeks between the two treatment groups (FIRST vs. WL). A mixed ANOVA test will be used to measure the effect of emotional stroop task reaction time between T1 & T3. Means and standard deviations will be reported. The Statistical Analysis Plan will outline the analysis of all the other mechanism outcomes.

We do not anticipate that missing data will be more than what has been accounted for in the trial sample size estimation. The level and pattern of the missing data in the baseline variables and outcomes will be investigated. The likely causes of any missingness will be summarised. If data are missing at random, multiple imputation will be used. If, when the missing data are analysed, they present another pattern other than missing at random, we will explore other methods of imputation.

iv) Maintenance of effect will be assessed as an exploratory analysis. Clinical outcome data at 52-weeks will be compared to the 20-week trial final endpoint data to determine whether the FIRST group maintained the 20-week PCL-5 scores. The 52-week experimental arm data will also be contrasted with published treatment effect evidence from NICE recommended TF-CBT therapy at the same time point e.g. [58, 59].This evidence will be compared with FIRST maintenance of effect data to inform NHS dissemination decisions and possibly generate future research questions using FIRST in additional populations living with PTSD to broaden our understanding of the impact of FIRST.

# 12 Project management

## 12.1 Investigator expertise

Ten investigators continue in roles developed during the feasibility trial bringing expertise as follows: Co-PIs (Sturt/Greenberg) bringing complex intervention trial delivery/PPI lead and occupational/military psychiatry expertise, PPI (Murray/Williams), FIRST therapy (de Rijk), psychological trauma (Armour), participant safety (Grealish), neurocognitive mechanisms (Tzouvara/Pile), trial management (Rogers), NHS veteran mental health services and support for assistant psychologists (Kreft), statistician (Fiorentino) and KCL Nightingale-Saunders Clinical Trials Unit supports the trial. Two colleagues, Dr Sharon Stevelink and Bethany Croak, join the team with their expertise in veteran women's mental health and PPI in this group as well as Amy Salford from Walking With The Wounded who brings the veteran charity perspective alongside her extensive clinical experience working in the complex mental health field

## 12.2 Project delivery

The co-principal Investigators, Sturt and Greenberg, will assume overall responsibility for the research. We will establish four project delivery sub-groups with defined remits. These are (1) Proof of Concept and main trial set-up sub-group which holds responsibility for ensuring regulatory approvals, developing the recruitment campaign, setting-up the study website, staff recruitment, KCTU database development, establishing the oversight committees; (2) Therapy delivery sub-group with responsibility for therapist recruitment and training, therapy delivery, quality assurance and participant safety; (3) Mechanisms sub-group with responsibility for the timely development and delivery of the mechanisms work-package and (4) Main trial delivery sub-group which will evolve out of the POC sub-group once the main trial begins and will ensure the timely delivery of the RCT. These groups will meet monthly and each will be chaired by a member of the Investigator team. A fifth sub-group, Knowledge Transfer, will focus on the upscaling of therapy delivery and

therapist training. This will begin meeting once the main RCT trial is underway and is expected to meet bi-annually.

During the internal pilot phase, core research members from the Main trial delivery sub-group will begin to meet fortnightly to monitor recruitment to all study elements and amplify the recruitment campaign as necessary. This group will have standing agenda items relating to participant safety, profile of participants related to diversity, data completion, intervention commencement and the detection and management of adverse events. Other team members will attend by request of the PI as required. All sub-groups will report to the Project Management Group which links directly into, and out from, the PPIE group.

### 12.3 Project Management Group

The whole research team will form the Project Management Group (PMG), consisting of investigators, collaborators and two members of our public involvement group. The committee will meet three times per year and report to the Trial Steering Group (TSC).

### 12.4 Oversight Committees

A data monitoring and ethics committee will be appointed (DMEC) and both this and the Trial Steering Committee (TSC) will meet at key milestones. The TSC will be chaired by Dr Lawrence Astill-Wright, a psychiatrist who has expertise in reconsolidation research in PTSD. The DMEC will be chaired by Dr Sara Tai who chaired this during the feasibility trial and membership will include an independent clinical expert and an independent statistician. The DMEC will be responsible for assessing safety and efficacy and making recommendations to the TSC. The study's statistician will write reports for the DMEC who will have unmasked access to all data. If the DMEC have concerns about the safety of the RCT, they will discuss the results in the report with the TSC in a joint meeting.

### 12.5 Patient and Public Involvement Committee

We have an established patient and public involvement group that has supported our trials during the feasibility through to the current FIRST PETT. PPIE member Shepherd, will chair the meetings and alongside co-applicant Murray, will attend the PMG. With the support of co-investigators Stevelink and Croak, we will increase female representation within the group by running a recruitment campaign within their established veteran women's mental health public engagement groups. The PPIE will meet bi-annually and will provide feedback via email at other times. Members will be compensated at a rate of £25.00 per hour.

## 13 End of study definition

End of study is defined as data base lock.

## 14 Assessment of safety

The safety of potential and actual participants is the greatest ethical concern. Our feasibility safety protocol performed well and we have strengthened it to address the safety needs of ineligible participants and participants in the Waiting List (WL) arm of the study (Appendix 1).

Participant safety will be a standing agenda item on every fortnightly core research team sub-group meeting throughout the Proof of Concept and RCT.

Our DMEC will meet once during the POC and up to four times during the full trial and comprises two trauma experts, as well as an independent statistician. An interim analysis of the data will take place mid-way through the RCT. The DMEC terms of reference will operate according to the King's Clinical Trials Unit Standard Operating Procedures. The research team will report any participant safety issues to the DMEC within 48 hrs of each fortnightly King's and Queen's meeting.

Participant mental health safety including symptom severity and deterioration will be assessed

using the PCL-5 self-report screening questionnaire at the beginning of every therapy session until discharge. The PCL-5 will also be assessed at all data collection timepoints (baseline, six-weeks, 12-weeks, 20-weeks and 52-weeks) alongside the PHQ-9, which assesses for depression and risk of self-harm. The research team will review all incoming follow-up PCL-5 and PHQ-9 scores within 72 hours of receipt.

### 14.1 Adverse events

PTSD Adverse Events are defined as a ≥10 point rise in the self-report PCL-5 since the previous therapy session or a 15 point rise from baseline or the maximum score of 80 being reached and/or relapse into alcohol and/or substance misuse at a hazardous level which integrated with the clinical judgement of the treating therapist will determine the action taken.

Self-harm adverse events are defined as responding 1 or above on the PHQ-9, question 9 and

### 14.2 Serious adverse events

PTSD Serious Adverse Events are defined as hospital admission for mental ill-health, self-harm, suicide and attempted or completed suicide.

### 14.3 Care escalation procedures

If the participant is in therapy, Inspire will hold responsibility and clinical governance accountability for the participant's mental health and wellbeing, including their own safety and where relevant the safety of others and including the safeguarding of children and vulnerable adults. If at point of referral or during the course of treatment, Inspire therapists become concerned about the welfare of any participant or immediate family member they will escalate their concerns through Inspire's standardised risk assessment, escalation, management and safeguarding policies and procedures. Where necessary they will contact the participant's GP to mobilise referral to crisis response, NHS primary or secondary care. Likewise, if a safeguarding and vulnerable adults concern is identified this will be escalated, acted on and reported to the relevant statutory body – safeguarding team.

Before the participant is referred to Inspire and after discharge, the participant's GP holds responsibility and accountability for the participant's mental health and wellbeing and this includes their safety. If the participant scores on the PCL-5 indicate an adverse event, the unmasked researcher responsible for participant safety will make contact with the participant within six hours of noting the rise in score and encourage them to contact their GP and/or case worker. They will advise the participant that they will need to contact the participants GP and/or case worker to alert them to the rise in PTSD symptoms. The research team will review all incoming follow-up PCL-5 and PHQ-9 scores within 72 hours of receipt.

All AE will be recorded and reported to the study PI within 72 hours and will be discussed at the bi-weekly research core-team sub-group meeting. A report will be included in the TSC reporting for review.

A Serious Adverse Event that occurs following discharge from Inspire but whilst in the trial will be investigated by one of the study's senior investigators (i.e. Sturt or Greenberg) using Inspire's SAE investigational policies and procedures. The investigational report will be submitted to the DMEC chair.

The DMEC chair will be notified within 24 hours of the research team being notified of all serious adverse events.

All AE and SAE and the clinical and research team actions will be logged in the Trial Management File.

# 15 Ethics and regulatory approvals

## 15.1 Regulatory approvals

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 the King's College London Research Ethics Committee.

The trial will be registered with an international registry.

The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor

## 15.2 Confidentiality and anonymity

Each participant's personal details will be linked to a study identifier (pseudonym) and recorded in an encrypted and password protected online excel spreadsheet that three members of the research team will have access to. This file will be held on a secure KCL server. The stored therapy videos will need to show the participant's face but will be encrypted and stored using the pseudonym. We will not keep the recordings any longer than is necessary to adhere to therapy fidelity and audit requirements. Once this is confirmed the recordings will be destroyed. Participant consent will be sought for this. All data processing will be GDPR compliant and conform with standardised risk assessment, escalation, management and safeguarding policies and procedures. We are aware of the particularly sensitive nature of mental health and military veteran status in this population. These procedures were acceptable to veteran participants in our feasibility trial.

# 16 Success criteria and barriers to proposed work

Key success criteria are *recruiting to target* for the trial and mechanisms study (N=215). Military-related memorials, domestic news items and international conflicts are highly sensitive contexts for veterans and can impact negatively on help seeking behaviours. The launching of the social medial recruitment campaign will be informed by horizon scanning for these contexts and we will work closely with PPI members and collaborator Nativve to optimise the campaign. The *delivery of therapy* at the time agreed following participant randomisation is essential to keep the commitments to transparency and trustworthiness that our PPI members have stressed upon us. A key deliverable to enable this is having twelve therapists available and with capacity. We will work closely with collaborator Inspire and trainer/supervisor de Rijk to manage therapist capacity and attrition.

# 17 Intellectual Property and Commercialisation

FIRST uses background IP developed and owned by co-applicant de Rijk over 15 years delivering reconsolidation and NLP interventions for PTSD. Background IP developed during the feasibility trial and RfPB grant NIHR204566, owned by KCL, will be used in the protocol. Dr Rijk, through her companies Awaken Consulting and Awaken School will provide KCL with a licence for the use of her third-party background IP during the trial and for subsequent use of NHS implementation of FIRST.

# 18 Dissemination, outputs and anticipated impact

A report for the NIHR EME Programme will be produced and two Open Access publications to high impact journals on the trial and the mechanisms studies. NHS veteran, mental health and psychological trauma conferences will be targeted for national and international conference presentations. Dissemination plans are supported via KCL communications team's media

engagement and a trial website and Twitter account. A dissemination event will be held with invited stakeholders including, the general public, NHS managers, charity managers, therapists, veterans and their families, UK policy makers and elected Members of Parliament. The event will also be available online to increase participation across the UK.

### 18.1 Outputs

If findings warrant, a FIRST training centre will be developed and delivered at KCL to support the upscaling of FIRST therapy for PTSD within the NHS. Building on the efficacy findings and the ongoing RfPB NIHR204566 project, an HTA trial will be proposed according to the following PICO: in people with employment-related PTSD (e.g. NHS, social care, police, first responders, military workforce) (P), is FIRST (I) compared to usual care (C), cost-effective (O) in reducing PTSD symptoms by an MCID at 24 months (T).

## 19 Funders

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## 20 Signatures

To be signed by Chief Investigator minimum and statistician if applicable.

05/07/2024

_____ _____

Chief Investigator Date

Print name: Jackie Sturt

_____ __15 July 2024_____

Statistician (if applicable) Date

Print name: Francesca Fiorentino

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# 22 Appendices

## 22.1 Appendix 1: Participant safeguarding protocol

The safety of potential and actual participants is the greatest ethical concern. Our feasibility safety protocol performed well and we have strengthened it to address the safety needs of ineligible participants and participants in the Waiting List (WL) arm of the study.

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

The following comprises our safety protocol for all participants in the trial: those randomised to receive the Intervention immediately, those who are placed on the WL to receive FIRST in 20 weeks' time and those that withdraw. It addresses lines of responsibility and accountability, definitions relating to safety, escalation and safeguarding procedures in the event of notable clinical deterioration with or without an escalation in risk, alongside ensuring the safe and effective management of participants who are ineligible to enter the trial.

**1.0 Lines of responsibility and accountability**

1.1 Up until the point at which a participant has undertaken their eligibility confirmation assessment with King's contracted Assistant Psychologists (AP) and before their details are forwarded to Inspire on randomisation and for therapy appointments to be allocated, the participant's GP holds responsibility and accountability for the participant's mental health and wellbeing and this includes their safety.

1.2 For those participants randomised to receive FIRST therapy immediately (the Intervention arm) from the point at which the participant's details are handed over to Inspire to arrange their therapy sessions through to the point of discharge, Inspire have responsibility and clinical governance accountability for the participant's mental health and wellbeing and including their own safety and where relevant the safety of others and including the safeguarding of children and vulnerable adults.

1.3 From the point of discharge from Inspire therapy to the point of 52-week follow-up or withdrawal from the trial, the Intervention participant's GP holds responsibility and accountability for the participant's mental health and wellbeing and this includes their safety.

1.4 For those participants randomised to receive FIRST therapy in 20 weeks (the Control arm) up until therapy begins the participant's GP continues to hold responsibility and accountability. At the point therapy delivery with Inspire begins at 20-weeks until the point of discharge approximately four weeks' later, Inspire have responsibility and clinical governance accountability. Once therapy is completed for these participants, they are discharged from Inspire and their time in the study is complete. Responsibility for the participant's mental health and wellbeing returns to their GP.

1.5 Participant safety will be a standing agenda item on every fortnightly core research team sub-group meeting.

1.6 Data Monitoring and Ethics Committee (DMEC) will meet once during the Proof of Concept trial and four times during the full trial and comprises two trauma experts and an independent statistician. The DMEC terms of reference will operate according to the King's Clinical Trials Unit Standard Operating Procedures. The research team will report any participant safety issues to the DMEC within 48 hours of each fortnightly core research team sub-group meeting.

## 2.0 Definitions related of safety

2.1 Mental health safety - symptom severity, deterioration is assessed using the PCL-5 self-report screening questionnaire completed by the participant at the beginning of every therapy session until discharge. Any existing or emergent safeguarding and or vulnerable adult concern will be assessed and monitored at each session with proportionate action taken in accordance with legislative reporting requirements.

2.2 Mental health safety is assessed using the PCL-5 and PHQ-9 (question 9) self-report screening questionnaires completed by the participant at the following time points following FIRST therapy discharge (intervention arm), or while awaiting therapy commencement at 20-weeks (control arm): 6 weeks post randomisation, 12 weeks post randomisation, 20 weeks post randomisation and 52 weeks post randomisation (for those in the intervention arm).

- 2.2.1 The named researcher will review all incoming follow up PCL-5 and PHQ-9 scores within 72 hrs of receipt.
- 2.2.2 If PHQ9, Q.9 (risk of self-harm) is scored 1-3 this will trigger a safety contact email correspondence from the assessors (see 4.0).

2.3 PTSD Adverse Events are defined as a ≥10 point rise in the self-report PCL-5 since the previous therapy session or a 15 point rise from baseline or the maximum score of 80 being reached and/or relapse into alcohol and/or substance misuse at a hazardous level which integrated with the clinical judgement of the treating therapist will determine the action taken.

2.4 The risk of Self-Harm Adverse Event is defined as when the research team has been unable to make contact with the participant (see 4.5) on three separate occasions and contact is made from the research team to the participant's GP.

2.5 PTSD Serious Adverse Events are defined as hospital admission for mental ill-health, self-harm, suicide and attempted or completed suicide.

## 3.0 Safety net procedures for between therapy and follow up time points

3.1 All participants will be offered a *Contact Card* at the point of randomisation. This will list the contact details of services to call 24/7 if they feel they need to talk with someone about their mental health outside of their therapy session and throughout their trial participation. Contact details will include Lifeline, Samaritans and their GP and where appropriate their Aftercare case worker and Inspire's 24/7 helpline.

- 3.1.1 For participants in therapy, the therapist will record participant self-reports of all contacts being made in the therapy safety log.
- 3.1.2 For participants in follow up, the researcher will note such self-reports in the data collected and ask the participant for details. Details, if provided, will be recorded in the researcher's participant safety log.
- 3.1.3 The unblinded researcher will review the therapy database weekly to determine if any activity has been logged in the previous seven days.

## 4.0 Care escalation procedures in the event of a risk of self-harm reported on the PHQ-9

4.1 If the participant self-reports thoughts of self-harm on the PHQ-9, by answering 1-3 on question 9, the safety contact communication will be triggered.

4.2 On identifying a score of 1-3 on Q9, the research team assessor will contact the participant to ask them about their response and to suggest they may wish to speak to their GP for support.

4.3 If the research team assessor is unable to make contact or do not hear back from the participant within 24 hours, they will send a follow-up email.

4.4 If research team assessor still receive no response, they will send a third communication saying they have emailed the participant twice over the past two days and if they do not hear from them within 24 hours they will get in touch with their GP to let them know that they are concerned about them.

4.5 If this final communication does not elicit a response, the research team assessor will escalate the reporting and contact the GP, to voice our concerns. This will be reported to one of the study's senior investigators (Sturt or Greenberg) and be registered as an adverse event.

**5.0 Care escalation procedures in the case of adverse event**

5.1 If at point of referral or during the course of treatment, Inspire therapists become concerned about the welfare of any participant or immediate family member they will escalate their concerns through Inspire's standardised risk assessment, escalation, management and safeguarding policies and procedures. Where necessary they will contact the participant's GP to mobilise referral to crisis response, NHS primary or secondary care. Likewise, if a safeguarding and vulnerable adults concern is identified this will be escalated, acted on and reported to the relevant statutory body – safeguarding team.

5.1.1 The PCL- 5 will be completed at each therapy session. If ≥10 point rise in PCL-5 score occurs since the previous therapy session, or 15-point rise from baseline, or the maximum score of 80 is recorded on the PCL-5, they will use their clinical judgement to assess whether escalation is appropriate.

5.1.2 Any ≥10 point rise in PCL-5 score that occurs since the previous therapy session, or 15-point rise from baseline, or the maximum score of 80 recorded on the PCL-5, will be detected by the unblinded member of the research team (investigator Grealish) who will inform the DMEC chair within three working days.

5.2 If a participant's PCL-5 score rises by ≥10 points from the previous follow up, or 15-point rise from baseline, or the maximum score of 80 is recorded on the PCL5, the unblinded researcher (investigator Grealish) will make contact with the participant within six hours of noting the rise in score and encourage them to contact their GP and/or their case worker. They will advise the participant that the researcher will need to contact the participant's case worker (or GP if no case worker) to alert them to the rise in PTSD symptoms.

**6.0 Care escalation procedures in the case of serious adverse event**

**6.1** A serious Adverse Event that occurs during therapy will be investigated by Inspire according to their standardised clinical protocols and clinical governance framework.

6.1.1 The serious adverse event will be investigated by Inspire's clinical lead or delegated representative using Inspire's standardised SAE procedures - template and within an agreed time-frame contingent on the nature and seriousness of the event.

6.1.2 The completed investigation report will include recommendations, shared learning and corrective actions each to be completed within a specified time frame, presented to and signed off by the Inspire CEO – Board alongside being shared with the DMEC chair for review.

**6.2** A Serious Adverse Event that occurs following discharge from Inspire but whilst in the trial will be investigated by one of the study senior investigators (i.e. Sturt and Greenberg) using Inspire's SAE investigational policies and procedures. Inspire protocols and timeframes will be used. The investigational report will be submitted to the DMEC chair.

**6.3** The DMEC chair will be notified within 24 hrs of the research team being notified of all serious adverse events.

## 7.0 Ineligible participants

7.1 King's trained and contracted assistant psychologists – under supervision from a Consultant Clinical Psychologist (investigator Kreft) will determine whether each participant meets the inclusion and exclusion criteria.

7.2 During the eligibility confirmation assessment the assistant psychologist will complete a risk assessment, including the PHQ-9, and if the participant discloses suicidal ideation, the assistant psychologist will discuss this with their supervisor and/or a senior member of the research team to decide what action to take.

7.3 Those assessed as ineligible for the study will be signposted to alternative specialist voluntary or statutory services. We will provide a safety signposting flyer with contact details for emergency numbers, military organisations and charities that provide support, and offer tailored individual signposting, where appropriate.

7.4 For those ineligible, but assessed as high risk, the GP will be contacted to, where necessary, mobilise crisis response and potential referral to NHS primary or secondary care.

7.5 Where safeguarding and vulnerable adult's concerns are identified this will be escalated, acted on and reported to the relevant statutory body – safeguarding team.

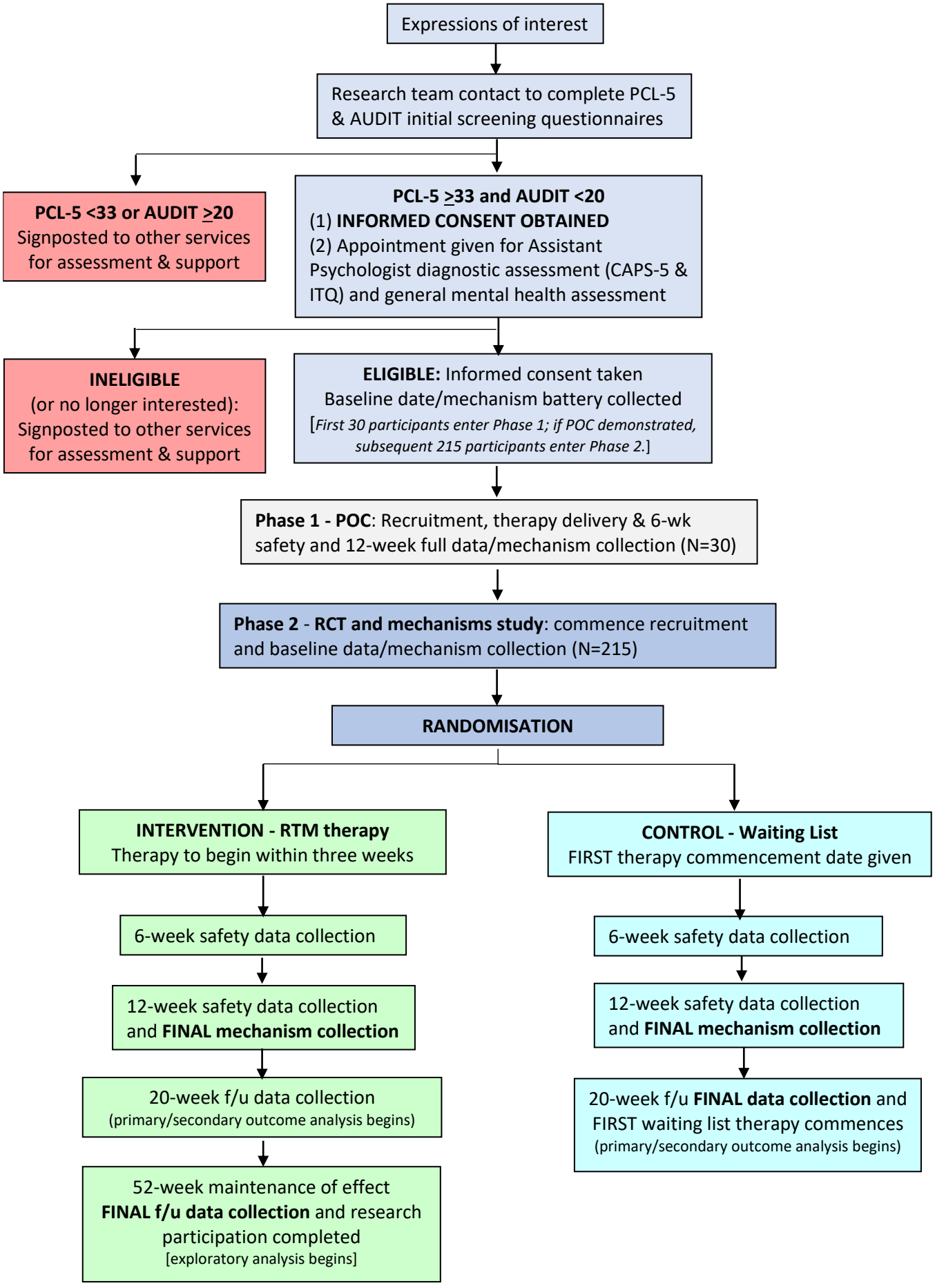
7.6 For any individual deemed at immediate high risk and who is unable to keep themselves safe, emergency services will be contacted directly.

## 8.0 Participants that withdraw

8.1 Participants that join the study are free to withdraw at any point. In this circumstance responsibility and accountability for the participant's mental health and wellbeing revert or remain with the participant's GP.

8.2 Once the research team is aware of the participant's withdrawal they will contact the participant to thank them for taking part in the study and will provide them with the contact details of alternative specialist voluntary or statutory services. They will provide a safety signposting flyer with contact details for emergency numbers, military organisations and charities that provide support, and offer tailored individual signposting, where appropriate.

## 22.2 Appendix 2 Participant and data flow diagram



## 22.3 Appendix 3 FIRST PETT detailed project plan - 48 month trial

| Months | 1-2 | 3-4 | 5-6 | 7-8 | 9-10 | 11-12 | 13-14 | 15-16 | 17-18 | 19-20 | 21-22 | 23-24 | 25-26 | 27-28 | 29-30 | 31-32 | 33-34 | 35-36 | 37-38 | 39-40 | 41-42 | 43-44 | 45-46 | 47-48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Feb/Mar 24 | Apr/May 24 | Jun/Jul 24 | Aug/Sep 24 | Oct/Nov 24 | Dec 24/ Jan 25 | Feb/Mar 25 | Apr/May 25 | Jun/Jul 25 | Aug/Sep 25 | Oct/Nov 25 | Dec 25/ Jan 26 | Feb/Mar 26 | Apr/May 26 | Jun/Jul 26 | Aug/Sep 26 | Oct/Nov 26 | Dec 26/ Jan 27 | Feb/Mar 27 | Apr/May 27 | Jun/Jul 27 | Aug/Sep 27 | Oct/Nov 27 | Dec 27/ Jan 28 |
| **Pre-trial set up** | | | | | | | | | | | | | | | | | | | | | | | | |
| **KCL Ethics (submission deadline 23rd April)** | | | | | | | | | | | | | | | | | | | | | | | | |
| **POC SAP development** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Full SAP development** | | | | | | | | | | | | | | | | | | | | | | | | |
| **KCTU database development** | | | | | | | | | | | | | | | | | | | | | | | | |
| **FIRST therapy staff recruitment (10-12)**<br>**FIRST AP recrutitment (10)** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Research staff recruitment** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Therapist train/supervision/wash-in** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Assistant Psychologist trial specific training with Josh** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Social media campaign development** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Project management** | | | | | | | | | | | | | | | | | | | | | | | | |
| **PMG meetings**<br>**(F2F in London/Belfast)** | | | | | | | | | | | | | | | | | | | | | | | | |
| **PPI meetings** | | | | | | | | | | | | | | | | | | | | | | | | |
| **TSC/DMEC meetings** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Feasibility trial & clinical trial & mechanism study** | | | | | | | | | | | | | | | | | | | | | | | | |
| **POC pilot (s3 months) – recruit (R), therapy delivery (T), 12-wk data collection (D), analysis (A), report (R)** | | | | R(N=30 12+12 (24) | R 10 (30) | T | D/A/R | | | | | | | | | | | | | | | | | |
| **Recruitment, eligibility assessment, informed consent & randomisation**<br>**with five month internal pilot (N=50)** | | | | | | | | | | | | | | | | | | | | | | | | |
| **FIRST Therapy commencement & delivery** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Baseline and final follow up assessments inc. mechanisms at 20 weeks post & 52-wk maintenance of effect** | | | | | | | | | | | | | | | | | | | 20 D | | | 52 D | | |
| **Post-trial** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Data cleaning** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Trial site close-down** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Data analysis** | | | | | | | | | | | | | | | | | | | | | 20 week | | 52 week | |
| **Reporting/Dissemination** | | | | | | | | | | | | | | | | | | | | | | | | |