Study Protocol

Enhanced Skills Training in Affective and Interpersonal Regulation (ESTAIR) vs. Treatment as Usual (TAU) for Complex Posttraumatic Stress Disorder (CPTSD) in Military Personnel: A Pilot Study

Sponsor/School	School of Health and Social Care Edinburgh Napier University 9 Sighthill Court Edinburgh EH11 4BN
Chief Investigators	Prof. Thanos Karatzias & Dr Dominic Murphy
Co-investigators	Prof. Mark Shevlin Dr Walter Busuttil
Funder	Forces in Mind
Funding Reference Number	FiMT19/0429EDU
Ethical Approval Number	SHSC2686062, amended and approved 27th July 2021
Project Start Date	1st January 2021
Project End Date	30th April 2023

NCT number: NCT04752072

BACKGROUND AND RATIONALE

The 11th version of the *International Classification of Diseases* (ICD-11) (WHO, 2018), produced by the World Health Organization (WHO), includes two trauma-based disorders; PTSD and Complex PTSD. The description of PTSD in ICD-11 is simpler than that provided within the DSM-5. In contrast to the 20 symptoms spread across four symptom clusters in DSM-5, ICD-11 PTSD includes just six 'core' symptoms across three clusters, each of which is directly related to one's traumatic exposure: re-experiencing in the here and now (Re: 2 symptoms), avoidance (Av: 2 symptoms), and a sense of current threat (Th: 2 symptoms). Diagnosis of ICD-11 PTSD requires the presence of one symptom per cluster, plus evidence of functional impairment. CPTSD is a broader diagnosis that includes the core PTSD symptoms plus an additional set of symptoms that are collectively referred to as 'disturbances in self-organisation' (DSO). These symptoms are intended to capture pervasive psychological disturbances associated with traumatic exposure and are distributed across three clusters: affective (hyper-activation and hypo-activation) dysregulation (AD), negative self-concept (NSC), and disturbances in relationships (DR). A CPTSD diagnosis requires that the PTSD criteria be met in addition to endorsement of symptoms from each of the DSO clusters.

Evidence from clinical samples (Karatzias et al., 2017) as well as population-based samples (Karatzias et al., 2019) suggests that CPTSD is a more common condition than PTSD in the UK. Although comparisons between general populations and military populations are lacking, in a recently completed cohort study (n=178) of a veteran help-seeking population in Combat Stress, it was found that 56% met diagnostic criteria for CPTSD versus 14% who met criteria for PTSD (Murphy et al., 2020). Identifying effective interventions to treat veterans with CPTSD is therefore of paramount importance.

Nevertheless, CPTSD is a new condition and there are currently no validated treatments available to aid recovery from this debilitating condition. One recent metanalytic review (Karatzias et al., 2019b) suggested that existing interventions, commonly used for PTSD, such as Cognitive Behavioural Therapy (CBT) or Eye Movement Desensitisation and Reprocessing (EMDR) can be less useful for CPTSD symptoms, if there is history of childhood trauma. It is now well known that high rates of childhood trauma are common amongst military samples (Murphy et al., 2018). It is also well established that veterans with PTSD appear to profit less from current 'gold standard' treatments for PTSD than other trauma populations (Bisson et al., 2007, Phelps et al., 2018). A recent study demonstrated significant heterogeneity in veteran's treatment response to a standardized 6-week residential treatment program for PTSD; 27.5% were treatment resistant with no decrease in PTSD symptom severity, and 45.7% had moderate improvements. These groups who responded poorly to standard treatment were characterised by having higher baseline levels of PTSD, higher levels of anxiety and depression, and combat experience (Murphy et al., 2018); which might denote presence of CPTSD. Similarly, a study of the effectiveness of an accredited PTSD outpatient treatment programme for Australian veterans showed that high levels of baseline PTSD and other psychological problems, depression, and guilt, were predictors of poor treatment outcome. Again, it is likely that the poor responders were suffering from CPTSD rather than simple PTSD. Finally, evidence on the usefulness of phased interventions, which has previously been advocated as the gold standard for CPTSD, has also been questioned (Mahoney et al., 2018).

Emerging evidence suggests that it is imperative that new treatments need to be developed and tested for CPTSD. Karatzias and Cloitre (2020) have proposed modular therapy as a new promising area of treatment enquiry for CPTSD and a new treatment protocol has been developed (Cloitre et al., 2019). The use of a flexibly applied multi-modular treatment approach is new to the trauma field signalling a treatment innovation and paradigm shift in research methodology. However, there is a good rationale for its application and a successful precedent in mental health that lays out a methodological road map for its testing. First, such approaches have been found to be more effective compared to use of full

standardised treatment protocols for conditions such as depression and anxiety (Daleiden et al., 2006). Second, modular therapies for depression and anxiety appear to have a second benefit for patients in that they tend to be shorter and so time and expense burdens on the patient (Weisz et al., 2012). Third and relevant to treatment uptake of evidence-based therapies, clinicians trained in a modular therapy versus those trained in disorder-specific manualized therapy (e.g. CBT for depression) showed improved attitudes about evidence-based practices (Borntrager et al., 2009). Moreover, clinicians reported greater satisfaction with modular treatments as compared to standard evidence-based treatments, and reported their assessment of them as more effective compared to usual care (unspecified), suggesting that modular treatments provide the "best of both worlds" with high ratings on both practitioner satisfaction and effectiveness (Chorpita et al., 2015). Modular therapy has never been tested in CPTSD before.

Until the ICD-11 proposed the distinction between PTSD and CPTSD in 2018, there was no way to reliably allocate trauma exposed help-seeking individuals to treatment tailored specifically to their needs. Those with complex presentations were subsumed within a general PTSD treatment population. This project provides the opportunity, for the first time, to evaluate the feasibility of delivering a tailored treatment programme for those veterans who meet the diagnostic criteria for CPTSD.

AIMS

ICD-11 CPTSD is a new condition and there are currently no identified effective treatments to enable recovery from this debilitating condition. Identifying effective interventions to treat veterans with CPTSD is therefore of paramount importance. We have recently proposed in the research literature a new innovative person-centred treatment approach for CPTSD (i.e. modular therapy; Karatzias and Cloitre, 2020). Enhanced Skills Training in Affective and Interpersonal Regulation (ESTAIR) involves targeting the symptoms of CPTSD clusters sequentially using concrete modules (i.e. specific number of sessions targeting specific clusters of symptoms). This intervention has never been tested in a military population before.

The project will provide information on recruitment and acceptability of a new treatment for CPTSD. The following main research questions will be addressed as part of this pilot project:

I. Is it feasible to recruit for a study on ESTAIR vs. TAU in military personnel during the study recruitment period?

II. What is the retention rate in the study at the end of treatment and at 3-month follow-up?

III. Are primary and secondary outcomes acceptable from participants?

IV. Is the new ESTAIR protocol acceptable by people with CPTSD?

STUDY DESIGN

To our knowledge, this is the first pilot trial in the world on the acceptability of modular therapy for veterans with CPTSD using a new treatment manual. The present study has been approved by Edinburgh Napier University (SHSC2686062).

A randomised trial design will be employed, adhering to the *Consolidated Standards of Reporting Trials* (CONSORT; Schulz, 2010). This study has been designed to confirm that we can successfully recruit and retain participants in a larger trial characterised by the same design parameters (e.g., allocation ratio, blind assessment, types of treatment and control

offered, multiple sites). The planned randomised pilot study is therefore a 28-month feasibility/pilot of a single site, single (rater) blind trial of ESTAIR (psychological intervention vs. treatment as usual (TAU) alone for the treatment of CPTSD using the ITQ as the primary outcome. In this study, participants will be randomly allocated to receive treatment as usual (TAU) or a psychological intervention (ESTAIR) to improve CPTSD symptoms.

Randomisation

Participants will be randomly allocated to group to minimize bias. Block randomisation will be used to ensure balanced assignment to the intervention and comparison group. Randomly permuted blocks (based on 12 blocks with 4 subjects per block) will be used to reduce the risk of predicting group assignment and ensure equal groups sizes. Randomised lists will be generated using an online, closed-source, web service (http://www.randomization.com/). Randomisation will be completed by Mark Shevlin.

STUDY POPULATION AND RECRUITMENT

Combat Stress received approximately 3400 veteran referrals across the UK between April 2018/2019. Based on a recently completed cohort study, it is predicted that about 1,900 will meet criteria for CPTSD. As such, potential participants will be recruited and screened via Combat Stress.

Potential participants will be drawn from those referred to the Southern Treatment Combat Stress Treatment Centre (Leatherhead). They will have completed a mental health assessment as part of the referral and registered with Combat Stress for treatment. Potential participants will meet criteria for CPTSD, as indicated by the ITQ completed during their initial assessment. All new referrals are discussed at a weekly case management meeting to determine eligibility based on the inclusion and exclusion criteria below:

Inclusion criteria

- Adults (18 years or older) in the caseload of Combat Stress
- UK armed forces veteran
- Help-seeking for trauma related psychological distress
- Meets diagnostic criteria for CPTSD as measured by the ITQ
- Proficiency in English language
- Signed informed consent provided

Exclusion criteria

- Severe psychotic disorder (defined by previous clinical diagnosis)
- Current alcohol or drug use disorder
- Serious cognitive impairment
- Planned concurrent additional treatment

Recruitment

When entering Combat Stress' clinical service, veterans are offered a formal assessment by a member of the multi-disciplinary team (MDT). As part of this process, they complete various psychometric measures of health including the International Trauma Questionnaire (ITQ). All cases are discussed at a weekly case management meeting. The research assistant will be embedded within the clinical team at Combat Stress' treatment centre in Leatherhead, Surrey to facilitate recruitment for this study. Veterans meeting criteria for CPTSD on the ITQ and deemed ready for therapy by the MDT will be approached to participate in the study.

The following procedure will be followed to recruit participants for the study:

1. The research assistant will attend the case management meeting to screen veterans for eligibility for the study.

2. If eligible, the research assistant will approach potential participants by letter and will be sent the patient information sheet and consent form. This invitation will be followed up by telephone call by the research assistant to discuss questions about the study and to discuss participants' willingness to participate. At this meeting, it will be emphasised that participation is voluntary.

   Note: Due to the COVID-19 pandemic, the patient information sheet and consent form letter will be sent to potential participants via email, and they will later receive a printed copy by post.

3. If willing to participate, participants will be asked to attend a one to one or on-line meeting with the research assistant. At this meeting they will be asked again if they have any questions about the study, sign the consent form and complete pre-treatment measures. All forms can also be returned via mail. Following this, they will be randomised to one of the two groups (TAU or ESTAIR).

4. The research assistant will then inform Combat Stress of the outcome so participants in the TAU or who opted out can be offered the standard treatment.

STUDY INTERVENTIONS

Enhanced Skills Training in Affective and Interpersonal Regulation (ESTAIR) (Cloitre et al., 2019)

ESTAIR will be offered according to the protocol (Cloitre et al., 2019) by an experienced psychotherapist appointed for the study and trained to its delivery. Treatment sessions will be conducted individually. ESTAIR will consist of up to 25 sessions organised in 4 modules of about 6 sessions each tackling the symptoms of PTSD and DSO symptoms. The first initial session is a formulation session to link present difficulties and traumatic life events, discuss current issues and concerns, and collaboratively agree on relevant treatment goals.

ESTAIR entails a flexible application of tools that match participants' specific needs. The PTSD module provides narrative exposure to the traumatic memories and targets re-experiencing, avoidance, and hyperarousal symptoms. The AD module focuses on identifying and labelling feelings, emotion management, distress tolerance, and acceptance of feelings and experiencing positive emotions. The NSC module focuses on how to stay in the present moment and combat dissociation; self–compassion and mindfulness skills; challenging thinking patterns and developing a balanced view of self. The DR module focuses on exploration and revision of maladaptive schemas; effective assertiveness; awareness of social context; and flexibility in interpersonal expectations and behaviours that are displayed in social interactions.

Update Note: During the training of the psychotherapist in the ESTAIR intervention, slight modifications to the treatment protocol were made.

1. Given the pilot nature of the present study, it was determined that the modules would be delivered in a sequential manner, starting with the AD module, the DR module, the NSC module, and then finishing with the PTSD module if necessary.

2. It was determined that the ESTAIR protocol still consists of up to 25 sessions, starting with the initial formulation session and ending with the final summary and

relapse-prevention session. However, the number of sessions per module were modified from up to 6 sessions per module, to up to 5, 6, 5 and 7 sessions for the AD, DR, NSC and PTSD modules, respectively.

3. Given the decision to offer modules sequentially (see point 1 above), session 25 (summary and relapse-prevention) was modified. In order to avoid repetition of the content of final session of the PTSD module (that summarizes the client's work in relation to PTSD symptoms) and session 25 (that summarizes the client's work across all ESTAIR modules), it was decided that for the purposes of the present pilot it would be more suitable to extend the time allotted for the final PTSD module session to incorporate additional content of session 25.

Defined completers will be those who have a valid post-treatment assessment using the ITQ at the end of every module and are diagnosis free. The ITQ will be administered at the end of every module and if the person is CPTSD diagnosis free then they will be offered a full post-treatment assessment. Subsequent input from Combat Stress following completion of trial will be offered as required and as per normal service standards.

Update Note: The ITQ will be administered at the end of every module to inform clinician's understanding of veteran difficulties. Participants will receive all four treatment modules, and dropping below CPTSD diagnosis on the ITQ at the end of a module will not serve as an indication to end treatment. Treatment will run include all four modules, unless strong clinical rationale to not do so.

Treatment Fidelity

The ESTAIR intervention will be administered by an experienced psychologist who will be trained in ESTAIR delivery. The therapist will be supervised by TK for the duration of the study. A selection of treatment sessions will be video-taped and assessed for treatment integrity and fidelity.

Update Note: All treatment sessions will be video-taped. A selection of tapes of 8 participants will be made to assess treatment integrity and fidelity. Treatment integrity and fidelity will be assessed according to the ESTAIR treatment fidelity checklist.

Treatment as Usual (TAU)

At present there are no recommended treatments for CPTSD. TAU will normally consist of receiving a mental health assessment by either a psychiatrist or psychologist. Following this, a treatment package will be developed that could include elements of psychoeducation, symptom-management, and trauma-focused cognitive behaviour therapy. Details of TAU interventions delivered for all participants in the TAU will be recorded.

Update Note: TAU will consist of receiving a mental health assessment by a mental health professional.

OUTCOME MEASURES

Outcomes are as follows: **(i)** Retention & data completion rates at weeks 25 weeks post-treatment and 12-week follow-up, on the primary outcome; International Trauma Questionnaire (Cloitre et al., 2018) and secondary outcomes: PHQ Depression (Kroenke et al., 2001), GAD Generalised Anxiety (Spitzer et al., 2006), AUDIT Substance Misuse (Saunders et al., 1993), and PHQ-15 Medically Unexplained Symptoms (Kroenke et al., 2002) **(ii)** 12-month recruitment rate; **(iii)** participant & clinical staff views on trial & intervention

acceptability and suggested changes. Baseline information on demographics including age, gender, marital status etc., will be gathered to characterise the sample.

A range of assessments will be administered by the research assistant to test the acceptability of primary (PTSD and CPTSD) (i.e. ITQ) and secondary outcomes (depression, anxiety, alcohol use, and somatisation) (e.g. GHQ-12, AUDIT). Participants in both groups will be asked to complete these outcome measures at baseline, after 25-weeks post-treatment and then again after at a 12-week follow-up. The ITQ will be also completed by the ESTAIR group at the end of every module. In addition, data will be recorded on retention and DNA rate. The research assistant will be masked to group allocation to demonstrate to future funders this is achievable in a future trial.

Note: The ITQ will be completed by the therapist and participant at the end of every model. Due to feasibility concerns, the research assistant will not be masked to group allocation when collected measures at baseline, post-treatment, and follow-up. This is not expected to have any impact on outcomes as all primary and secondary outcome measures are self-report.

Primary Outcome

The International Trauma Questionnaire **(**ITQ; Cloitre et al., 2018). Six items represent the three clusters of PTSD: Re-experiencing, Avoidance, and Sense of Threat. CPTSD includes PTSD as well as three clusters reflecting Disturbances in Self-Organisation (DSO); Affective Dysregulation (AD), Negative Self-Concept (NSC), and Disturbances in Relationships (DR), all captured by 16 items. The endorsement of symptoms is scored on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely), indicating how much a symptom has affected them in the past month. The Likert scores can be recoded into six binary variables that in turn demonstrate meeting criteria for ICD-11 PTSD or CPTSD based on scores greater than 2. A diagnosis of PTSD requires endorsing at least one symptom in each of its three clusters as well as functional impairment. A diagnosis of CPTSD requires PTSD and endorsement of at least one of the three DSO clusters plus functional impairment.

Secondary Outcomes

Depression

Nine symptoms of depression are measured by the *Patient Health Questionnaire-9* (PHQ-9; Kroenke et al., 2001). Respondents indicate how often they have been bothered by each symptom over the last two weeks using a four-point Likert scale ranging from 0 (*Not at all*) to 3 (*Nearly every day*). Possible scores range from 0 to 27, with higher scores indicative of higher levels of depression. To identify participants likely to meet the criteria for depressive disorder, a cut-off score of 15 was used as it has been reported that this score produces specificity of .96. The psychometric properties of the PHQ-9 scores have been widely supported.

Generalized Anxiety

Symptoms of generalized anxiety are measured using the *Generalized Anxiety Disorder 7-item Scale* (GAD-7; Spitzer et al., 2006). Like the PHQ-9, respondents indicate how often they have been bothered by each symptom over the last two weeks on a four-point Likert scale (0 = *Not at all*, to 3 = *Nearly every day*). Possible scores range from 0 to 21, with higher scores indicative of higher levels of anxiety. The GAD-7 has been shown to be a reliable and valid measure in multiple studies.

Alcohol Use

The presence of an Alcohol Use Disorder (AUD; Saunders et al., 1993) will be measured using the AUDIT-C, a brief self-report measure comprised of the first three questions of the *Alcohol Use Disorders Identification Test*. The clinical utility of the AUDIT-C has been demonstrated in multiple samples including the general population, military veterans, and hospitalised patients. Scores on the AUDIT-C range from 0-12, and based on a nationally representative sample of adults from the United States, scores ≥ four effectively capture a DSM-5 diagnosis of AUD.

Somatic Symptoms

Medically unexplained symptoms will be assessed using the *Patient health Questionnaire-15* (PHQ-15; Kroenke et al., 2002). The scale includes the most prevalent DSM-IV somatization disorder somatic symptoms. Participants are required to rate the severity of 13 symptoms as 0 ("not bothered at all"), 1 ("bothered a little"), or 2 ("bothered a lot"). Responses are coded as 0 ("not at all"), 1 ("several days"), or 2 ("more than half the days" or "nearly every day") to produce total scores ranging from 0 to 30 and scores of ≥5, ≥10, ≥15 represent mild, moderate and severe levels of somatization. The reliability and validity of the PHQ-15 are acceptable.

Update Note: Friends and Family Test (FFT). The FFT was added as an additional secondary measure to help infer the acceptability of the ESTAIR intervention in comparison to TAU. The FFT is a single item asking participants to indicate 'how likely is it that you would recommend our service to your GP, family and friends if they needed similar care?'. Responses are indicated on a 5 point-Likert scale ranging from 1 ('Extremely unlikely') to 5 ('Extremely likely'). The FFT is standardly administered as an end-of-treatment measure at Combat Stress.

Additional Outcomes

The *Life Events Checklist* (LEC; Gray, Litz, Hsu, & Lombardo, 2004) is a 17-item self-report measure for potentially traumatic events in the respondent's lifetime. The LEC assesses exposure to 16 events plus one item assessing any other extraordinarily stressful event. The respondent checks whether they (a) directly experienced, (b) witnessed, (c) learned about, (d) are not sure, and (e) does not apply to them. The LEC has demonstrated adequate reliability and validity. The LEC is administered at baseline assessment only.

The *Moral Injury Outcome Scale* (MIOS; Litz et al., 2020) is a 15-item self-report measure of moral injury. Respondents indicate how much they would agree with certain statements (e.g., "I feel like I don't deserve a good life" and "I have lost faith in humanity)" over the past month. Agreement is indicated on a 5-point Likert scale ranging from 0 ("Strongly disagree") to 2 ("Neither agree or disagree") to 4 ("Strongly agree"). Possible scores range from 0 to 60, with higher scores indicating greater severity of moral injury. The MIOS is administered at baseline and follow-up.

Update Note: Due to further work on validating the MIOS, one item was removed resulting in a 14-item self-report measure of moral injury.

Adverse Events

No severe adverse events have been reported of previously used versions of ESTAIR with people with complex trauma, including in randomised controlled trials (Cloitre et al, 2010). However, we wish to improve the recording and reporting of adverse effects of psychological interventions and have therefore developed a robust protocol for assessing and managing any such risk, which will be completed at end of treatment and at follow-up. The Adverse Events Questionnaire (AEQ; Hutton et al., 2015) was initially developed to investigate adverse effects of a psychosis-specific intervention and was adapted for the present study by removing any psychosis-specific items.

The AEQ used in the present study consists of 25 items (e.g., worsening of mental state, heightened stigma, increased medication use), which are responded to on a 5-point scale ranging from “Not at all” to “Very much”. All participants completing the ESTAIR intervention will complete the trial-completer, patient-rated version of the AEQ. To improve on the reporting of adverse events, participants who withdraw from the study will be asked to complete the early-withdrawal version of the AEQ together with the therapist.

Using an approach applied previously (adapted from Klingberg et al., 2012), we will define serious adverse events as (i) death by suicide; (ii) suicide attempt; (iii) suicidal crisis without attempt; (iv) severe symptom exacerbation (increase of 2 standard deviations or more on the patient or researcher-rated ITQ. Non-severe adverse events will be defined as a score of ≥3 (agree ‘quite a lot’ or ‘a lot’) on any item on the AEQ (Hutton et al., 2015).

Qualitative outcomes

Qualitative data will be collected to explore the acceptability of the ESTAIR intervention. It was initially intended to invite a total of 4 completers and 4 non-completers from the ESTAIR arm to participate in a one-off qualitative interview. In order to enhance understanding of the acceptability of ESTAIR and to manage feasibility concerns, it was decided that all participants in the ESTAIR arm would be asked to answer specific, brief questions assessing their experience of the protocol, their perception of treatment in general, and suggestions for improvement.

PROCEDURE

Potential participants will be screened by the MDT team, and eligible participants will be contacted by the research assistant. As previously described in the ***Recruitment*** section above, eligible participants will be provided with the patient information sheet and consent form. Potential participants will be contacted by the research assistant, who will ensure that they have received an information sheet and will answer any questions. All potential participants will be reminded that participation is entirely voluntary and that deciding not to take part in the study will have no impact upon the clinical care they receive. They will also be informed of their right to withdraw from the study at any time, without giving a reason, and reassured that exercising their right to withdraw will have no impact upon the ongoing care they receive. Potential participants who wish to take part will need to provide informed consent. Participants who are not eligible or who do not want to participate will be offered routine care as per Combat Stress procedures.

Eligible participants who provide consent to take part will complete baseline measures and will then be randomized to either the ESTAIR or TAU intervention arm. At 25-weeks (post-treatment), participants will be contacted by the research assistant to complete post-intervention measures. Participants in the ESTAIR arm will also be asked to provide qualitative data of their experience of intervention. The research assistant will then set an appointment to again contact participants in 12-weeks’ time to complete the follow-up measures.

Participant Withdrawal or Discontinuation

Participants are free to withdraw from the study at any point, without giving any reason and without their legal rights or usual care being affected. Investigators may also withdraw participants if they deem their continuation to be harmful. The trial management group will review all instances of adverse events, whether they are judged to be attributable to the trial or interventions, and, based on this information, determine whether the participant should be withdrawn. Non-identifiable data from participants who have been withdrawn will be used to assess the feasibility of the study.

Participant engagement may be discontinued based on adverse events. In the instance of an adverse event, the clinician will inform the trial management group. The trial management group will review this form and determine whether the event could reasonably be attributed to the intervention or participation in the trial. The trial management group will review all instances of adverse events, whether or not they are judged to be attributable to the trial or interventions, and, based on this information, determine whether the participant should be withdrawn and/or whether the trial should be suspended, stopped or continued.

Update note: In addition to informing the study's trial management group, a protocol has been developed to appropriately address any concerns regarding the client's safety. The protocol involves informing and seeking supervision from Combat Stress' senior clinical staff and safeguarding leads, liaising with the client's GP, and potential involvement of local crisis teams if necessary. Any identified adverse events or concerns regarding risk will also be brought to the attention of Combat Stress' MDT team for relevant input.

Study Suspension or Discontinuation

The research project would be stopped in the event of several therapy-attributable adverse events. Any serious adverse events will be passed on to trial management group for review, who would have responsibility for assessing whether they are attributable to study participation, setting the threshold for discontinuation and issuing advice to suspend or discontinue. This advice would be acted upon by the researchers, in consultation with the Sponsor.

ESTAIR participants will continue treatment until (1) the clinical aims have been met, where the clinician deems 'reliable recovery' has occurred, or (2) the criteria for withdrawal have been met (4 or more missed sessions).

Update note: The criteria for withdrawal has been extended to include if participants do not attend 4 or more sessions in total or two continuous sessions, in the absence of any exceptional circumstances.

Progression Criteria for a Full Trial

We will progress for a full trial if we achieve our target recruitment and acquire post-intervention (25 weeks) ITQ data from ≥75% of those randomised.

STATISTICAL CONSIDERATIONS

Sample size

There are currently no effectiveness studies on the psychological interventions for CPTSD to enable power calculations. Following a pragmatic approach and in line with previous pilot studies in the area of PTSD we will aim to recruit n=30 individuals per arm (total sample = 60). This approach will enable us calculating sample size for an adequately powered trial.

Data analysis

Recruitment and Retention

Recruitment and retention rates at all stages of the trial will be recorded and summarised as counts and percentages.

Quantitative analyses

The main analyses of the trial data will conducted in 2 phases; (1) modelling within-subject changes in ITQ scores for data from the ESTAIR arm of the trial and a (2) comparison

between the ITQ scores, and secondary outcome measures, for the ESTAIR and TAU groups at 25 weeks and 12 week follow-up.

Phase 1: An analogue to a repeated measures ANOVA will be specified as a structural equation model to handle missing data efficiently using robust maximum likelihood estimation (MLR: Schafer & Graham, 2002) and relax assumptions about the variance-covariance structure of the observations (Hoffman, 2015). An initial model will specify and estimate a model with the mean ITQ scores from the five observation periods (baseline, 7, 13, 19, 25 months) constrained to be equal, and then the model will be re-estimated with the means to be freely estimated. The difference in model fit can be tested using the loglikelihood difference test, which is distributed as a chi-square ($\chi 2$). A significant $\chi 2$ result indicates that the unconstrained model is better than the constrained model, meaning that the null hypothesis of equal means can be rejected (Hoffman, 2015). If this is the case pairwise differences in means will be tested using the Wald $\chi 2$ test. The magnitude of the change in symptoms scores will calculated using Cohen's d with a correction for repeated measures designs (drm). Values < 0.40 reflect 'small' effects, values from 0.40 to 0.79 reflect 'medium' effects, and values > 0.80 reflect 'large' effects.

Phase 2: The primary intention to treat analysis will conducted to examine differences between the ESTAIR and TAU groups at 25 weeks. This analysis will be conducted using a regression approach, simultaneously regressing the 25 week mean scores of the ITQ, PHQ-9, GAD-7, PHQ-15, and AUDIT onto a dummy-coded binary variable representing the treatment and control group (ESTAIR = 1, TAU =0). The estimated regression coefficient for each variable indicates the mean difference between the treatment and control group, and the associated p-values indicate statistical significance. This approach was used as (1) all the model parameters are estimated simultaneously thereby avoiding the need for post-hoc adjustment for multiple testing, (2) the use of robust maximum likelihood (MLR) estimation allows for missing data to be handled efficiently by using all available data (Schafer & Graham, 2002), and third, MLR estimation is robust against deviations from normality and produces unbiased standard errors (West, Finch, & Curran, 1995). Furthermore, the standardised regression coefficients from this model can be used as a useful analogue to Cohen's d as a measure of effect size (Nieminen, Lehtiniemi, Vähäkangas, Huusko, & Rautio, 2013): d=0.20 is a 'small' effect, d=0.50 is a 'medium' effect, and d=0.80 is 'large' effect size.

Qualitative analyses

Qualitative data regarding acceptability of the intervention and the outcomes will be recorded and summarised. Qualitative data will be analysed using the thematic analysis guidelines (Braun & Clarke, 2006).

OPERATIONAL CONSIDERATIONS

Risks associated with research

Assessment and management of increased distress

Some of the non-clinical research procedures (interviews and questionnaires) involve divulging personal and sensitive information in relation to current symptoms and mood, including suicidal ideation. In relation to symptoms, the questionnaires and measures to be used in this study (ITQ, GAD, PHQ) are routinely used in healthcare practice, without reported adverse effects.

Prior to study commencement, the research assistant will be fully trained on how to respond to any increased distress. During the study, they will receive weekly supervision by

experienced clinical psychologists, who will also be directly contactable by phone during the research interviews. If the participant experiences mild distress, the RA will stay with them until any distress subsides. They will listen empathically and will help them to arrange contact with their clinician. If their distress is more severe the RA will immediately contact their supervisor for instruction. As far as possible, participant appointments for assessments will be scheduled alongside their clinical appointments so clinicians are available. All participants will be provided with contact details for relevant support organisations in the unlikely event that they feel distressed after leaving the appointment. They will also have the contact details of the RA should they have any further questions following the study. Participants will be regularly reminded that they are free to withdraw from the study at any point, without providing a reason and that their usual treatment will remain unaffected. Therapy sessions will be provided by an experienced therapist and any distress that might arise during therapy will be dealt with as per normal clinical practice.

Management of disclosures (harm to self or others)

The study involves questions about traumatic stress, which is associated with self-harm. As people will have regular contact with a clinician for their treatment, an imminent risk of harm to self or others will already be known and managed appropriately. However, in some cases the clinical team may not be aware of this risk. In all cases, participants will be informed that their data will be held confidentially but if they disclose information which suggests an imminent risk of harm to them or someone else, then the research team are obliged take steps to reduce this risk, which in most cases will involve them sharing their concerns immediately with their GP who will then take over the clinical management. The research assistant will act at all times under supervision of an experienced clinical psychologist in assessing and managing this process, ensuring both they and the participant are fully supported and safe.

Burden of non-clinical (research) procedures

For ethical and pragmatic reasons, we have designed the assessments to involve as less burden as possible. We have minimised the number of assessment points and have carefully selected our measures to avoid duplication and gather only essential information.

The initial consent process and assessment of research capacity will take approximately 30 minutes. The initial baseline assessment (week 0) will take approx. 60mins to complete. Self-rated assessments will be used.

Researchers and clinicians

Meetings with participants will be conducted at Combat Stress venues or on-line through a secure platform. If therapy is conducted face to face, the research assistant and clinician will be aware of the safety measures available in treatment rooms (i.e. alarm buttons). The supervision team will be contactable throughout in the case that support or advice is required. In addition, clinical oversight for the project will be provided by Dr Walter Busuttil (Psychiatrist and Director at Combat Stress).

There is a small risk of researchers or clinicians being involved in an accident while travelling for the purposes of research. We will encourage all researchers who are required to travel as part of this project to use safe forms of transport (own vehicle or public transport) and to plan their journeys carefully to ensure their and others' safety. Outward travelling for research purposes will not be allowed before 7am or after 4pm. We will require all researchers to allow sufficient time for travelling to and from meetings, to avoid accidents as a consequence of haste.

Vicarious trauma

There is a small risk of research staff or clinicians experiencing vicarious trauma, whereby listening to participants describe their own traumatic events has a secondary emotional effect on them. All research and clinical staff will receive regular supervision and support from experienced clinical psychologists (the Chief Investigators). A standing item on the supervision agenda will be self-care, and supervisors will monitor – and encourage staff to self-monitor - for any signs of distress. By careful management of the flow of participants, we will ensure the research and clinical caseloads of all staff are shared equally, and we will suspend recruitment if there is any sign of the research or clinical staff feeling stressed or anxious because of demands. We will also encourage the research team to provide each other with social support, and researchers will be encouraged to seek help from their GP or occupational health should mental health problems emerge (whether related to the study or not).

Ethical considerations and good clinical practice

Ethical Conduct

This study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). Before the study commences, all required approvals will be obtained and any conditions of approvals will be met.

Investigator Responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks will be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

Informed Consent

For potential participants entering the study, the research assistant will discuss the study with them, answer any questions, give them an information sheet, and seek their consent to pass on their details to the research team.

Data Recording

All research and clinical staff will receive full training data quality, secure data management, maintaining confidentiality and record-keeping.

Good Clinical Practice (GCP) Training

Although GCP training is not a mandatory requirement for non-CTIMP studies such as this one, all research staff with contact with participants or patient identifiable data will be encouraged to complete this before handling data, recruitment of participants or assessments.

Confidentiality

Anonymized patient outcome data from the study will be stored on Combat Stress and University computers for data analysis. These computers are password protected. All hard copies of completed questionnaires used in the study will be made anonymous using a coding system and any personal identifiable information will be removed. These will be scanned and

stored in an encrypted format on a secure University password-protected computer system. Participant consent forms will contain names, contact details and identification code of the participant so that relevant questionnaire scores can be matched to the same participant. These will be scanned and stored in an encrypted format in a separate file on a secure Combat Stress password-protected computer system and will not be removed from Combat Stress premises.

Clinical procedures (therapy sessions), non-clinical procedures (research assessments and qualitative interviews) will be audio-recorded with participant consent, using encrypted and password secured audio recording devices. This is to enable (a) checks on therapy fidelity by the clinical supervisor (b) accurate ratings of interview responses by the research assistant and their supervisor and (c) transcription and analysis of qualitative interviews. Any personally identifiable data, including recordings and consent forms, will not leave Combat Stress premises and will be stored in line with the procedures above. Anonymized data (i.e., database of questionnaire scores, linked to anonymous participant ID, will be held in secure password-protected storage on Combat Stress or University computers. Anonymized and password-protected data may be shared by email within the Research Team, for the purpose of statistical analysis.

Only the informed consent forms and audio recordings will contain any participant identifiable data. Completion of the consent form will link the participant to a unique identification code which will be attached to all subsequent data (questionnaires and recordings). Data is not anonymous as such but will not be traceable to any particular individual unless access to the consent form is obtained. The list of codes and consent forms will be kept separately from one another in a different encrypted and password protected file on a secure Combat Stress computer system. Only the lead researchers and researchers with direct participant contact will have access to the file. All data will be held securely and treated in accordance with the BPS (2009) Code of Ethics and Conduct and BPS (2014) Code of Human Research Ethics guidelines documents and the study will adhere to the principles of Good Clinical Practice.

STUDY CONDUCT RESPONSIBILITIES

Protocol Amendments

Any changes in research activity, which involve a change in the study protocol (except those required to manage an urgent safety issue), will be reviewed and approved by the Chief Investigator. All study amendments will be submitted to a Sponsor representative for review and authorization.

Serious Breach of Protocol Requirements

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental wellbeing of the participants in the study; or

(b) the scientific value of the study.

If a potential serious breach is identified by the Chief investigator or delegates, the Sponsor will be notified within 24 hours. The Sponsor will assess the impact of the breach on the scientific value of the study, to determine whether the incident constitutes a serious breach and report to the ethics committee as necessary.

Study Record Retention

All patient identifiable information (audio files, consent forms, participant details) will be kept for a minimum of 6 months from the protocol defined end of study point, and a maximum of

12 months. All other study documentation will be stored for 10 years, in order to substantiate the research finding, and in adherence to Edinburgh Napier University policy.

End of Study

The end of study is defined as the last participant's last research meeting with a participant. The Investigators or the co-sponsor(s) retain the right at any time to terminate the study for clinical or administrative reasons.

Continuation of Treatment/Care Following the End of Study

The psychological intervention being tested is designed as a stand-alone discrete intervention and is considered to be complete after 25 sessions. Some of the strategies that participants being taught in ESTAIR can be used as an ongoing source of support. Following the end of the study, participants in both groups will receive appropriate support from Combat Stress as required.

Insurance and Indemnity

The following arrangements are in place to fulfil the Sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Sponsor/s require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

Management and governance

The Principal Investigators (PIs) will be Professor Thanos Karatzias (Edinburgh Napier University) and Dr Dominic Murphy (Combat Stress & King's College London). Dr Murphy will be responsible for overseeing clinical care and emergency clinical input if necessary. Co-investigators will be Professor Mark Shevlin and Dr Walter Busuttil (Combat Stress).

Edinburgh Napier University, as an established academic institution, complies with all appropriate national and international research delivery standards (e.g. ethics, data storage etc.). All research activity will be managed and monitored by the University Research Information Office (RIO). A RIO dedicated officer in the School of Health & Social Care, where the proposed work will be hosted, will monitor delivery, expenditure and adherence to agreed deadlines and will ensure all necessary agreements will be in place prior to start of the project. Combat Stress carries out research within an established Clinical Governance infrastructure. The Combat Stress national clinical governance group meets quarterly and reports quarterly to the Medical Services Committee (MSC), which is led by Trustees who have a medical background and this committee reports to the Board of Trustees. The MSC is chaired by Dr Suzy Walton a Senior Clinical Psychologist.

Day to day business will be the responsibility of a research team consisting of clinicians and academics who have conducted numerous studies to completion on traumatic stress in civilian and military populations. Prof. Karatzias is a clinical psychologist who is based in Edinburgh Napier University and NHS Lothian Rivers Centre for Traumatic Stress. He has extensive experience in conducting clinical trials for psychological trauma. Dr Murphy is a clinical psychologist who is based at Combat Stress and King's College London. He is widely published within the field of military mental health and has extensive experience collecting

research data from military populations. He is the president of the UK Psychological Trauma Society and member of NATO's Research Task Groups (RTG). Prof. Shevlin is based in Ulster University and he is also an expert in advanced statistical techniques relating to traumatic stress. Prof. Shevlin will oversee the analysis from the study and will advise on methodological aspects during its delivery. Dr Walter Busuttil will provide clinical oversight for the project and act as the medical advisor.

REFERENCES

Bisson, J.; Ehlers, A.; Matthews, R.; Pilling, S.; Richards, D.; Turner, S. (2007). Psychological treatments for chronic post-traumatic stress disorder: systematic review and meta-analysis. *British Journal of Psychiatry*, 190, 97-104.

Borntrager, C. F., Chorpita, B. F., Higa-McMillan, C., & Weisz, J. R. (2009). Provider Attitudes Toward Evidence-Based Practices: Are the Concerns with the Evidence or with the Manuals? *Psychiatric Services*, 60, 677–681.

Braun, V. & Clarke, V. (2006). Using thematic analysis in psychology. Qualitative Research in Psychology, 21;3(2):77–101.

Chorpita, B. F., Park, A., Tsai, K., Korathu-Larson, P., Higa-McMillan, C. K., Nakamura, B. J., . . . The Research Network on Youth Mental Health. (2015). Balancing effectiveness with responsiveness: Therapist satisfaction across different treatment designs in the Child STEPs randomized effectiveness trial. *Journal of Consulting and Clinical Psychology, 83*(4), 709-718.

Cloitre, M., et al (2010). Treatment for PTSD related to childhood abuse: A randomized controlled trial. *American Journal of Psychiatry*, *167*, 915-924. doi: 10.1176/appi.ajp.2010.09081247

Cloitre, M.; Shevlin, M.; Brewin, C.; Bisson, J.; Roberts, N.; Maercker, M.; Karatzias, T. Hyland P. (2018). The International Trauma Questionnaire: Development of a self-report measure of ICD-11 PTSD and Complex PTSD. *Acta Psychiatrica Scandinavica*, 138, 536 – 546.

Cloitre, M., Karatzias, T., Mc Glanaghy, E. (2019). Enhanced STAIR Narrative Therapy for CPTSD. Treatment Manual. Unpublished Manuscript.

Daleiden, E. F., Chorpita, B. F., Donkervoet, C., Arensdorf, A. M., & Brogran, M. (2006). Getting better at getting them better: Health outcomes and evidence-based practice within a system of care. *Journal of the American Academy of Child & Adolescent Psychiatry*, *45*, 749- 756.

Hoffman, J. I. (2015). Biostatistics for practitioners: an interpretative guide for medicine and biology. Elsevier Science & Technology.

Hutton P, Byrne R, Pyle M, Morrison AP. *Adverse Effects of Psychological Therapy Questionnaire*. Unpublished; 2015.

Hyland, P.; Shevlin, M.; Fyvie, C.; Karatzias T. (2018). Posttraumatic Stress Disorder (PTSD) and Complex PTSD (CPTSD) in DSM-5 and ICD-11: Clinical and Behavioural Correlates. *Journal of Traumatic Stress*, 31(2),174-180.

Karatzias, T., Shevlin, M., Fyvie, C., Hyland, P., Efthimiadou, E., Wilson, D.,……Cloitre, M. (2017). Evidence of distinct profiles of posttraumatic stress disorder (PTSD) and complex

posttraumatic stress disorder (CPTSD) based on the new ICD-11 Trauma Questionnaire (ICD-TQ). *Journal of Affective Disorders, 207,* 181-187.

Karatzias, T., Hyland, P., Bradley, A., Cloitre, M., Roberts, N. P., Bisson, J. I., & Shevlin, M. (2019). Risk factors and comorbidity of ICD-11 PTSD and complex PTSD: Findings from a trauma-exposed population based sample of adults in the United Kingdom. *Depression and anxiety*, *36*(9), 887-894.

Klingberg, S., Herrlich, J., Wiedemann, G., Wölwer, W., Meisner, C., Engel, C., ... & Wittorf, A. (2012). Adverse effects of cognitive behavioral therapy and cognitive remediation in schizophrenia: results of the treatment of negative symptoms study. *The Journal of nervous and mental disease*, *200*(7), 569-576.

Karatzias, T.; Murphy, P.; Cloitre, M.; Bisson, J.; Roberts, N.; Shevlin, M.; Hyland, P.; Maercker, A.; Ben-Ezra, M.; Coventry, P.; Mason-Roberts, S.; Bradley, A.; Hutton P. (2019b). Psychological interventions for ICD-11 Complex PTSD symptoms: Systematic review and meta-analysis. *Psychological Medicine*. 49, 1761 – 1775.

Karatzias, T., & Cloitre, M. (2019). Treating adults with complex posttraumatic stress disorder using a modular approach to treatment: Rationale, evidence, and directions for future research. *Journal of Traumatic Stress*, *32*(6), 870-876.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine*, *16*(9), 606-613.

Kroenke K, Spitzer RL, Williams JB (2002). The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosomatic Medicine*, 64, 258-66.

Mahoney, A.; Karatzias, T.; Hutton P. (2018). A systematic review and meta-analysis of group treatments for adults with symptoms associated with complex post-traumatic stress disorder. *Journal of Affective Disorders*, 243, 305 - 321.

Murphy, D., Shevlin, M., Pearson, E., Greenberg, N., Wessely, S., Busuttil, W., & Karatzias, T. (2020). A validation study of the International Trauma Questionnaire to assess post-traumatic stress disorder in treatment-seeking veterans. *The British Journal of Psychiatry*, *216*(3), 132-137.

Murphy, D. & Smith, K.(2018). Treatment efficacy for UK veterans with posttraumatic stress disorder: latent class trajectories of treatment response and their predictors. *Journal of Traumatic Stress*, 31, 753-763.

Nieminen, P., Lehtiniemi, H., Vähäkangas, K., Huusko, A., & Rautio, A. (2013). Standardised regression coefficient as an effect size index in summarising findings in epidemiological studies. Epidemiology, Biostatistics and Public Health, 10(4).

Phelps, A.; Steel, Z.; Metcalf, O.; Alkemade, N.; Kerr, K.; O'Donnell, M. et al. (2018). Key patterns and predictors of response to treatment for military veterans with post-traumatic stress disorder: A growth mixture modelling approach. *Psychological Medicine*, 48, 95-103.

Saunders, J. B., Aasland, O. G., Babor, T. F., & de la Fuente, J. R. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption: II. *Addiction*, 88(6), 791–804.

Schafer, J. L., Graham, J. W. (2002). Missing data: Our view of the state of the art. Psychological Methods, 7, 147–177.

Schulz K, Altman D, Moher D: CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010, 8: 18-10.1186/1741-7015-8-18.

Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine*, *166*(10), 1092-1097.

Weisz, J. R., Chorpita, B. F., Palinkas, L. A., Schoenwald, S. K., Miranda, J., Bearman, S. K., et al. (2012). Testing standard and modular designs for psychotherapy treating depression, anxiety, and conduct problems in youth: A randomized effectiveness trial. *Archives of General Psychiatry*, *69*, 274-282.

West, S.G., Finch, J.F., & Curran, P.J. (1995). Structural equation models with non-normal variables: Problems and remedies. In R. Hoyle (Ed.), Structural Equation Modeling: Concepts, Issues and Applications, (pp. 56-75). Newbury Park, CA: Sage.

World Health Organization. (2018). *International statistical classification of diseases and related health problems* (11th Revision). Retrieved August 2019 from https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f264310751