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Emotional freedom technique versus written exposure therapy versus waiting list for post-traumatic stress disorder: protocol for a randomized clinical MRI study

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Emotional freedom technique versus written exposure therapy versus waiting list for post-traumatic stress disorder: protocol for a randomized clinical MRI study

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**ABSTRACT**

**Introduction:** The emotional freedom technique (EFT) is a meridian-based psychotherapy that combines tapping on acupoints with cognitive reframing. Previously, small-sized studies showed a potential effect of EFT on post-traumatic stress disorder (PTSD); however, the clinical evidence and underlying mechanisms are still limited and unknown. This proposed clinical trial aims to examine the effect of EFT on patients with PTSD compared with the waitlist (WL) and active controls.

**Methods and analysis:** This study was designed as a randomized, assessor-blinded, three-arm clinical MRI study. A total of 120 eligible patients with PTSD will be recruited and randomized into EFT, written exposure therapy (WET), or WL groups. EFT and WET will be applied once a week for 5 weeks. For patients in the WL group, EFT will be performed after 12 weeks. PTSD symptoms, depression, anxiety, somatic symptoms, and quality of life will be evaluated. Assessments will be conducted at baseline (week 0), post-treatment (week 6), and follow-up (week 12). Structural and functional brain images and recording videos of facial expressions to emotional stimuli will be obtained before and after treatment. Sixty participants without lifetime traumatic experiences will be enrolled as healthy controls. The primary objective of the study is to compare the change from baseline in the Clinician-Administered PTSD Scale after treatment (week 6) between EFT and WL groups and between EFT and WET groups.

**Ethics and dissemination:** Ethical approval was obtained from the Institutional Review Board of the Kyung Hee University Korean Medicine Hospital. The research findings will be shared at national and international conferences and will be published in peer-reviewed journals.

**Trial registration number:** Clinical Research Information Service: KCT0007360


**Keywords:** Stress Disorders, Post-Traumatic; Emotional Freedom Technique; Magnetic Resonance Imaging; Randomized Controlled Trial; Clinical Protocols
Strengths and limitations of this study

- This will be the first randomized controlled trial to evaluate the emotional freedom technique for patients with post-traumatic stress disorder compared with the waitlist controls and written exposure therapy.
- This study will collect a wide range of data, including an assessment of clinical symptoms, questionnaires, recording videos of facial expressions to emotional stimuli, and structural and functional MRI, to investigate the underlying neurological mechanisms.
- Additionally, baseline characteristics and changes after treatment of patients with post-traumatic stress disorder will be examined in comparison with healthy controls without traumatic experiences.
- Because of the nature of psychotherapy interventions, participants and clinicians cannot be blinded to treatment allocation, and only assessors will be blinded.
INTRODUCTION

Background and rationale

Post-traumatic stress disorder (PTSD) is a disorder that occurs after exposure to traumatic events such as death, serious injury, or sexual violence. These symptoms include repetitive and painful memories of the traumatic event, intrusive symptoms such as dreams, persistent avoidance of stimuli associated with the traumatic event, negative changes in cognition and emotion associated with the traumatic event, and pronounced arousal and responsiveness associated with the traumatic event.\(^1\) According to the 2021 National Mental Health Survey conducted in Korea, the lifetime prevalence of PTSD is 1.5% (1.3% for men, 1.6% for women), and the annual prevalence is 0.3% (0.2% for men, 0.3% for women).\(^2\) PTSD often involves depressive, substance use, and anxiety disorders simultaneously.\(^3\)

Trauma-focused psychotherapy is the first-line treatment for PTSD.\(^4,5\) Strongly recommended treatments for PTSD include cognitive-behavioral therapy, cognitive processing therapy, cognitive therapy, and prolonged exposure therapy.\(^6\) Among the various psychotherapies for PTSD, exposure therapy is one of the most studied and well-established treatments.\(^7\) However, trauma-focused exposure therapy has a high dropout rate. A meta-analysis reported that 36% of patients who received trauma-specific treatment dropped out in clinical trials, and a dropout rate of 30% in real-world practice in the United States Veterans Health Administration Prolonged Exposure Training Program was similar.\(^8,9\) Two major reasons why veterans dropped out of trauma-focused psychotherapy were a lack of buy-in to treatment and too stressful course, which were mostly related to uncomfortable exposure to the past.\(^10\) Thus, effective and efficient therapy is required to increase compliance and remission in patients with PTSD.

The emotional freedom technique (EFT) is a meridian-based psychotherapy that combines tapping on acupoints and exposure to cognitive reframing.\(^11\) In reviews on the effect of EFT on patients who experienced traumatic events and were at a high risk of PTSD, 4–10 EFT sessions were effective for PTSD symptoms and were proven to be safe.\(^12,13\) Two randomized controlled trials reported that EFT is potentially effective in improving PTSD symptoms in patients who are diagnosed as PTSD.\(^14,15\) Karatrias et al. reported that after 8 weeks of EFT treatment, PTSD symptom levels decreased and persisted after a 3-month follow-up, which was not significantly different from those of eye movement desensitization and reprocessing (EMDR) treatment.\(^14\) In another study, Church et al. reported that a 4-week EFT treatment reduced PTSD symptom levels and psychological distress compared to the standard care wait list.\(^15\)
According to the assessment by the Korean Medicine Procedure Expert Assessment Committee on April 29, 2021, EFT using acupuncture point tapping was determined as a safe and non-invasive method for symptom improvement in PTSD compared to palliative treatment. However, it was pointed out that there is limited evidence and follow-up data of EFT in PTSD when compared with cognitive-behavioral therapy and EMDR, which are currently recommended as psychotherapies for the treatment of PTSD in textbooks and guidelines. The aforementioned randomized controlled trials have limitations in that both included a small number of participants (46 and 59, respectively) and used symptom-related parameters to assess efficacy. Therefore, further studies with a sufficient number of participants are necessary to examine the effectiveness of EFT in PTSD.

Before planning this trial, we conducted a feasibility trial of a 5-session EFT in 30 patients diagnosed with PTSD. In this before-and-after study, PTSD symptoms of participants generally improved after the EFT intervention, compliance with attending EFT sessions was high, and the dropout rate was low. In this trial, we selected written exposure therapy (WET) as an active control, as it is a short-term therapy that is adequate for comparison with 5-session of EFT. In addition, the waiting list was included as another control group, and this trial will be planned with a three-arm parallel design.

A critical limitation is that there are no well-established biomarkers related to either the diagnosis or prognosis of PTSD. Exploring the underlying mechanisms and seeking predictive factors that affect the response to PTSD treatments are also important, in addition to simply evaluating the efficacy of the treatment. To meet such demands, attempts have been made to identify biomarkers for PTSD using various methodologies. In comparison with non-trauma controls, patients with PTSD showed left amygdala hyperactivation, and in comparison with non-trauma controls and trauma-exposed controls, patients with PTSD exhibited diminished activation in the medial prefrontal cortex. In a longitudinal functional magnetic resonance imaging (fMRI) study, higher dorsal anterior cingulate cortex, insula, and amygdala activations in response to negative pictures was a predictor of poor response to PTSD treatment. In the present study, structural and functional brain images will be obtained before and after the intervention to explore the underlying mechanisms.

Objectives

The primary objectives are to evaluate the effect of EFT on PTSD symptoms compared to the waiting list (WL) and to evaluate the non-inferiority of EFT on PTSD symptoms compared to WET. The change from baseline in the Clinician-Administered PTSD Scale (CAPS-5) after the intervention will be compared between the EFT and WL groups and between the EFT and WET groups.
The secondary objectives are to evaluate the effect of EFT compared to WL and WET based on the proportion of loss of PTSD diagnosis and full remission of PTSD after the intervention. Additionally, self-reported PTSD symptoms will be evaluated using the PTSD Checklist-5 (PCL-5), and depression and anxiety will be assessed using the Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI). Quality of life will also be evaluated using the EuroQol-5 Dimension-5 Levels (EQ-5D-5L) and World Health Organization quality of life assessment instrument abbreviated version (WHOQOL-BREF).

The exploratory objective is to explore the biomarkers and predictors of PTSD diagnosis and prognosis. Structural and functional MRI, recording videos of facial expressions to emotional stimuli, blood samples, and various questionnaires related to gastrointestinal symptoms, empathy, and Korean medicine patterns will be longitudinally collected.

**Trial design**

This study is designed as a randomized, assessor-blinded, three-arm, parallel-group clinical MRI study. The 120 eligible patients with PTSD will be randomly allocated to the EFT, WET, or WL groups in a 1:1:1 ratio (Figure 1).

**METHODS AND ANALYSIS**

**Study setting**

This study will be conducted at a university hospital in Seoul, Korea.

**Eligibility criteria**

**Patients with PTSD**

The inclusion criteria will be women aged between 19 and 65 years; diagnosis of PTSD by Structured Clinical Interview for DSM-5 (SCID-5); symptoms of PTSD for >3 months, regular visits once a week for 6 weeks; and patients who voluntarily agree to participate.

Exclusion criteria will be risk of suicide; current or past history of schizophrenia or bipolar disorder; alcohol or other substance use disorders within 8 weeks; history of cerebrovascular diseases, brain tumor, or traumatic brain injury (participants with mild traumatic brain injury will not be excluded); history of neurological or systemic diseases that may affect the central nervous system; history of
acute infectious disease within 2 weeks; history of taking the following medications within 4 weeks; use of systemic steroids, antipsychotics, antidepressants, benzodiazepines, sleep medications (participants taking the medications in stable doses for >2 weeks will not be excluded); history of taking antibiotics within 2 weeks; vaccination within 4 weeks or plans for vaccination during the study period; moderate or higher cognitive impairment; medical conditions requiring inpatient treatment; receipt of medication or other interventions in other clinical trials within 1 month; current active psychotherapy; pregnant or lactating women; women who do not use medically acceptable contraception during the study period; those determined as unsuitable by the investigators.

Healthy controls

The inclusion criteria for healthy controls will be women aged between 19 and 65 years, those without traumatic experiences, those who do not meet the diagnostic criteria of PTSD according to the SCID-5, those who do not have functional/organic disorders and clinically meaningful findings in the history taking and physical examination, Patient Health Questionnaire (PHQ)-9 score ≤4, Generalized Anxiety Disorder Screener-7 score ≤4, PHQ-15 score ≤5, and those who voluntarily agree to participate.

The exclusion criteria for healthy controls will include a history of major mental disorders. The other exclusion criteria are shown the clinical study registration.

MRI-specific exclusion criteria

These exclusion criteria will be applied to patients with PTSD and the healthy controls: ferrous-containing metal substance within the body and difficulty tolerating enclosed, small spaces because of claustrophobia.

Interventions

EFT

EFT consists of five, 40-minute, weekly sessions that include tapping on acupoints and exposure to cognitive reframing. The EFT protocol for patients with PTSD was developed on the basis of previous studies. In the previous feasibility trial, a developed EFT protocol was applied to 30 patients with PTSD in Korea, and the mean PCL-5 score was decreased to -14.33 (95% confidence interval [CI]: -19.79, -8.86) points after the five sessions of EFT. In the first session, the therapist will
provide an introduction to EFT. In every session, EFT will be applied with the following procedures: check subjective units of distress; set up; sequence; 9 gamut sequence; repeat the sequence; and check changes in subjective units of distress. In the set-up procedure, the therapist and participant will make a “set-up statement,” which is one of the essential parts in EFT, and include exposure to trauma with cognitive reframing.

WET

WET consists of five, 40-minute, weekly sessions that focus on expressive writing about a traumatic event. We will follow the WET protocol developed by Sloan et al.\textsuperscript{17,18} This WET protocol was applied to patients with PTSD in Korea, and the severity of PTSD symptoms was alleviated after five sessions of WET.\textsuperscript{24} In the first session, therapists will introduce WET and select the trauma experience to be covered in this WET session. Before writing, the subjective units of distress (between 0 and 100) will be checked. Instructions for writing will be provided using the WET script, and participants will write about their trauma in detail for 30 minutes. From the second to the fifth sessions, specific writing instructions will be provided using the WET script, and 30 minutes of the writing session will be completed. EFT and WET will be applied by qualified therapists working at the Department of Neuropsychiatry in Korean medicine, who have completed exposure-based treatment and EFT or WET protocol training.

WL

The participants assigned to WL will not receive any intervention until completion of the follow-up visit. After 12 weeks, the follow-up visit and evaluation will be completed, and EFT will be applied to participants in the WL group.

Criteria for discontinuing or modifying allocated interventions

Participants will be considered for treatment cessation and elimination from the study if they meet following criteria: participants who do not meet the inclusion and exclusion criteria, participants with serious adverse events, participants with adverse events warranting discontinuation of the study intervention, participants with symptom aggravation and in need of another treatment, participants who withdraw consent, participants who are lost to follow-up, participants whose compliance with the intervention is <70%, participants who are unsuitable for continuing administration by the investigators.
Outcomes

Primary outcome

The primary outcome is the mean change from the baseline CAPS-5 score at week 6 (post-treatment). CAPS-5 is a representative clinician rating scale for PTSD. The CAPS-5 score will be measured at baseline, week 6 (post-treatment), and week 12 (follow-up). The mean change in CAPS-5 scores between baseline and week 6 will be the primary outcome.

Secondary outcomes

The mean change from the baseline CAPS-5 score at week 12 (follow-up), loss of PTSD diagnosis, and full remission rates at week 6 (post-treatment) and week 12 (follow-up) will be secondary outcomes used to assess the severity of PTSD symptoms. Loss of PTSD diagnosis and full remission of PTSD will be defined based on the results of CAPS-5. A total CAPS-5 score <20 will be defined as the remission of PTSD. Additionally, PCL-5 will be used as a self-rating scale to assess the severity of PTSD symptoms. BDI-II and BAI will be used to assess the severity of depression and anxiety symptoms, respectively. Additionally, PHQ-15 and the Insomnia Severity Index (ISI) will be used to assess the severity of somatic symptoms in patients with PTSD. To evaluate the quality of life in patients with PTSD, EQ-5D-5L and WHOQOL-BREF scores will be used as secondary outcomes.

Exploratory outcomes

Exploratory outcomes will be measured before and after the intervention (weeks 0 and 6). Structural and functional brain images will be obtained using 3T MRI. Emotional tasks that induce emotions of funny, anxiety, and sadness by watching video clips will be conducted, and the facial expressions of participants during the tasks will be recorded and analyzed. The pain and cutaneous sensory thresholds will be measured. In addition, various questionnaires, including the pattern identification questionnaire, empathy quotient, social network questionnaire, Toronto alexithymia scale, perceived stress scale, irritable bowel severity symptom severity scale, gut quotient, and gastrointestinal symptom rating scale, will be measured as exploratory outcomes. Figure 2 summarize the participant timeline.
Sample size

The sample size was computed to detect the mean difference in change from the baseline CAPS-5 score after treatment between the EFT and WL groups. No previous study has compared the CAPS-5 scores between EFT and WL. We estimated that EFT would have an effect size similar to that of EMDR, and in a previous study comparing EMDR with WL, the effect size (Cohen's $d$) of EMDR was 0.65. With a two-sided significance level of 0.05 and a power of 0.8, 38.14 participants are required in each group. Considering a dropout rate of 5%, 40 participants will be recruited per group, and a total of 120 will be investigated. The dropout rate was calculated based on a previous feasibility trial of EFT in patients with PTSD.

Recruitment

To achieve adequate participant recruitment, regular advertisements will be conducted through online media, and approved materials will be attached to the bulletin boards inside and outside of the hospital. In the case of delayed recruitment, local advertisement can be implemented.

Allocation

Random assignment will be performed in compliance with group assignments that are not biased and not exposed to participants and researchers. An independent statistician who is not involved in the performance and evaluation of this clinical trial generated a random assignment sequence in a 1:1:1 ratio for each group using blocked randomization in SAS® (version 9.4, SAS Institute Inc., Cary, NC, USA). The generated random sequence table will be kept by the independent statistician and protected from disclosure.

For each random number, the assignment results will be sealed in an opaque envelope and stored in a locked cabinet. Participants' random numbers will be assigned according to the order in which the participants are enrolled at visit 2 after the screening process. A random number will be given independently of the screening number. The corresponding envelope will be opened according to the random number, and group assignment will be performed. The date and time of opening and the signature of the researcher who opened it will be written on the open envelope and stored separately.
285 **Blinding**

286 The participants will be allocated to the EFT, WET, or WL groups, and it is impossible to blind therapists and participants during the intervention. Nevertheless, this study is designed as an assessor-blinded trial to control for bias as much as possible. Effectiveness and safety will be evaluated by independent assessors who have not performed the intervention procedure or random assignment. Visits for interventions (3–7) and assessment (2, 8, and 9) will be separated.

292 **Data collection methods**

293 To assess the severity of PTSD symptoms, the CAPS-5 and PCL-5 will be used. The CAPS-5 consists of 30 items measuring the severity of PTSD symptoms, and the total score ranges from 0 to 80, with higher scores indicating more severe symptoms. The validated Korean version of the CAPS-5 will be used. CAPS-5 will be evaluated by qualified investigators. To ensure the consistency of CAPS-5, an investigator meeting was conducted for training before study initiation. The PCL-5 consists of 20 items measuring the severity of PTSD symptoms in the DSM-5, and the total PCL-5 score ranges from 0 to 80, with higher scores indicating severe symptoms. The validated Korean version of the PCL-5 will be used. To assess PTSD and depressive symptoms during the intervention period, the PCL-5 and BDI-II will be measured every 2 weeks. The BDI-II consists of 21 items, and the total score ranges from 0 to 63, with higher scores indicating more severe symptoms. A validated Korean version of the BDI-II will be used. Even if a participant withdraws consent, efforts will be made to schedule an evaluation visit for the CAPS-5.

306 **Data management**

307 The source document data will be entered into the electronic Case Report Form (eCRF). The eCRF was developed using the iCReaT (internet-based Clinical Research and Trial) system provided by the Korea National Institute of Health. A data management plan was prepared before study initiation. Data specifications were defined and source documents for each data point were agreed upon. Investigators at the institute were trained for data entry and coding using the eCRF system. The data entered in the eCRF will be checked bimonthly after enrolment of the first participant.
Statistical methods

Analysis sets

The analysis sets will be defined as follows. 1) Full analysis (FA) set: Population that complies with the intention-to-treat principle, meets major inclusion and exclusion criteria, and has obtained at least one primary outcome assessment after the baseline assessment. 2) Per protocol set: Population within the FA set who have ≥80% compliance with the interventions, do not take any prohibited medications, and do not have major violations to the protocol. 3) Safety analysis set: Population consisting of all participants whose safety assessment has been made at least once since the randomized allocation.

Statistical methods for analyzing the primary outcome

This is a multi-arm parallel-group randomized trial and there are three hypotheses for the primary outcome. The first null hypothesis is that the mean change from baseline at week 6 in the EFT group will be the same as that in the WL group ($H_0: \mu_1 = \mu_2$, $H_1: \mu_1 \neq \mu_2$). A mixed-effect model repeated measure (MMRM) will be used, with group and time as fixed factors, and participant as a random factor. The mean difference and 95% CI between two groups and p-values will be presented. The first hypothesis aims to assess the effect size of EFT on PTSD symptoms compared with WL.

The second null hypothesis is that the mean change from baseline at week 6 in the WET group will be the same as that in the WL group ($H_0: \mu_3 = \mu_2$, $H_1: \mu_3 \neq \mu_2$). MMRM will be used as in the first hypothesis. From the results of the second hypothesis, the non-inferiority margin ($M$) will be defined. The lower the 95% CI of the mean difference between two groups will be. $M$

The third null hypothesis is that the mean change from the baseline at week 6 in the WET and EFT group will be greater than $M$ ($H_0: \mu_3 - \mu_1 > M$, $H_1: \mu_3 - \mu_1 \leq M$). The third hypothesis assesses the non-inferiority of EFT compared with WET, and $M$ calculated in the second hypothesis will be used. MMRM will be used, similar to the first hypothesis, but the significance level will be set to 2.5% since the non-inferiority test is one-sided.

The problem of multiple testing will be solved using the fixed sequence method. If the statistical result for hypothesis 1 is significant, the tests for hypotheses 2 and 3 will be performed. If the first null hypothesis were not rejected, tests for hypotheses 2 and 3 will not be performed. If the first null hypothesis is rejected and the test for hypothesis 2 is performed, in case that the statistical result for hypothesis 2 is significant, the test for hypothesis 3 will be conducted.
Statistical methods for analyzing the secondary outcomes

Continuous variables (mean changes in CAPS-5, PCL-5, BDI-II, BAI, PHQ-15, ISI, EQ-5D-5L, WHOQOL-BREF, and Clinical Global Impression scores) will be tested using the same method as for the primary outcome. Additionally, to compare the difference between before and after the intervention in each group, the Student paired t-test or Wilcoxon signed-rank test will be used. Repeated measures analysis of variance will be performed to test the interaction between group and time.

Binary variables (loss of PTSD diagnosis and full remission of PTSD) will be tested using logistic regression analysis. Odds ratios (95% CI) for the two groups will be presented. Hypothesis setting and multiple-testing problem-solving methods will be the same as those used for the primary outcome.

Statistical methods used to handle missing data

The primary outcome will be analyzed using MMRM. The MMRM considers missing data using the maximum likelihood, and does not require the process of replacing the missing data. In the case of an additional analysis of covariance, missing data will be replaced using the multiple imputation method.

Data monitoring

Considering the low risk of interventions and the study purpose, a data monitoring committee is not needed. An interim analysis is not planned. If intervention-related moderate or severe adverse events occur in >25% of all participants, the study will be stopped.

Harms

Adverse events will be carefully recorded at every visit, and the frequency, severity, and causality of the adverse events will be assessed in the three groups. Additionally, the suicide risk of the participants will be evaluated using the Columbia Suicide Severity Rating Scale.
374 **Auditing**

Monitoring will be conducted to verify that the clinical study data are accurate and complete, and that the clinical study is performed in accordance with the approved protocol and related regulations. Monitoring of clinical studies will be conducted through regular visits to the institute. The scope of monitoring will include compliance with the clinical study protocol, collection of appropriate and accurate data, obtaining informed consent, and recording adverse events. The monitor will check the eCRF, source documents, and essential documents during regular visits.

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**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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**ETHICS AND DISSEMINATION**

**Research ethics approval**

This study has been approved by the Institutional Review Board (IRB) of the Kyung Hee University Korean Medicine Hospital (KOMCIRB2021-11-005-001).

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**Protocol amendments**

Protocol modifications will be determined after sufficient discussion by investigators at the hospital and KIOM and will be applied to the study after obtaining approval for the amendment from the IRB. The current version of protocol is 1.5 (date: 2022-11-16).

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**Consent or assent**

Written informed consent will be obtained from all participants prior to screening. The principal investigator and sub-investigators, who are Korean medicine doctors in the hospital and delegated by the principal investigator, will provide information about the clinical study and obtain informed consent from the participants. Informed consent and a description of the study approved by the IRB will be used. Sufficient time and opportunity for the participants to ask questions about the details of the clinical study and to decide whether to participate will be provided. Additional consent
will be obtained for the collection and analysis of blood samples.

Confidentiality

The personal information of each participant will not be entered into eCRF, and the data of each participant will be collected under screening and random numbers.

Ancillary and post-trial care

Follow-up observation and online follow-up observation will be conducted at weeks 12 and 24. Compensation criteria and plans will be prepared for those who suffer harm from trial participation. The occurrence of adverse events will be assessed at every visit, and the required treatment and observation will be applied until the symptoms disappear.

Dissemination policy

The clinical study information and results will be registered with the Clinical Research Information Service. This study’s findings will be presented at conferences and published in peer-reviewed journals. The participant-level dataset will be uploaded to the Korean Medicine Data Repository (kmdr.kiom.re.kr) after study completion.
Author contributions

H Kim, SH Cho, Y Choi, Y Kim, and S Choi conceived the trial. YE Choi, O Kwon, D Kwon, and S Lee helped with study implementation. Y Choi and Y Kim completed the initial draft of the manuscript. O Kwon generated the randomization sequence and provided biostatistical advice and information. All authors designed the study and read, edited, and approved the final manuscript and supplementary files.

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Competing interests

None declared.

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Figure legends

Figure 1 Flow diagram.

LEC-5, Life Event Checklist for DSM-5; CTQ, Childhood Trauma Questionnaire; SCID-5, Structured Clinical Interview for DSM-5; C-SSRS, Columbia Suicide Severity Rating Scale; CAPS-5, Clinician-Administered PTSD Scale; CGI-S, Clinical Global Impressions-Severity scale; CGI-I, Clinical Global Impressions-Improvement scale; PCL-5, PTSD Checklist-5; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Index; PHQ-15, Patient Health Questionnaire-15; ISI, Insomnia Severity Index; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; WHOQOL-BREF, WHO QoL assessment instrument abbreviated version; EFT, Emotional Freedom Technique; WET, Written Exposure Therapy; WL, Waiting List

Figure 2 The schedule of enrolment, intervention and assessment.

1The participants assigned to WL will not receive any intervention until completion of the follow-up visit. After 12 weeks, EFT will be applied to participants in the WL group.

2The facial expressions will be recorded during the emotional task.

Pattern identification questionnaire, empathy quotient, social network questionnaire, Toronto alexithymia scale, perceived stress scale, irritable bowel severity symptom severity scale, gut quotient, and gastrointestinal symptom rating scale.

EFT, Emotional Freedom Technique; WET, Written Exposure Therapy; WL, Waiting List; CAPS-5, Clinician-Administered PTSD Scale; CGI-S, Clinical Global Impressions-Severity scale; CGI-I, Clinical Global Impressions-Improvement scale; PCL-5, PTSD Checklist-5; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Index; PHQ-15, Patient Health Questionnaire-15; ISI, Insomnia Severity Index; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; WHOQOL-BREF, WHO QoL assessment instrument abbreviated version
**Visit 1**
Screening
~2 weeks

**Screening:** Informed consent, Demographics, Medical history, Physical examination, Blood test, LEC-5, CTQ, SCID-5, C-SSRS, Eligibility assessment

**Visit 2**
Baseline
Week 0

**Baseline assessment:** CAPS-5, CGI-S, PCL-5, BDI-II, BAI, PHQ-15, ISI, EQ-5D-5L, WHOQOL-BREF, MRI, Emotional task, and other questionnaires

Total N: 120

**Visit 3~7**
Intervention
Week 1~5

**Randomization**

EFT
N=40

WET
N=40

WL
N=40

EFT or WET (Visit 3~7), PCL-5, BDI-II (Visit 4, 6)

**Visit 8**
Post-treatment
Week 6

**Post-treatment assessment:** CAPS-5, CGI-S, PCL-5, BDI-II, BAI, PHQ-15, ISI, EQ-5D-5L, WHOQOL-BREF, MRI, Emotional task, and other questionnaires

**Visit 9**
Follow-up
Week 12

**Follow-up assessment:** CAPS-5, CGI-S, PCL-5, BDI-II, BAI, PHQ-15, ISI, EQ-5D-5L, WHOQOL-BREF

**Visit 10**
Close-out
Week 24

**Close-out assessment:** PCL-5, BDI-II, BAI, PHQ-15, ISI, EQ-5D-5L, WHOQOL-BREF
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<th>Intervention</th>
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<td>~ -14 days</td>
<td>Visit 1</td>
<td>Visit 2</td>
<td>Visit 3 ~ Visit 7</td>
<td>Visit 8</td>
<td>Visit 9</td>
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**ENROLMENT:**
- Informed consent: X
- Eligibility screen: X
- Allocation: X

**INTERVENTIONS:**
- EFT: X X X X X
- WET: X X X X X
- WL):

**ASSESSMENTS:**
- CAPS-5: X X X
- CGI-S: X X X
- CGI-I: X X
- PCL-5, BDI-II: X X X X X
- BAI: X X X
- PHQ-15, ISI: X X X X
- EQ-5D-5L, WHOQOL-BREF: X X X
- MRI: X X
- Emotional task: X X
- Other exploratory questionnaires: X
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<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
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<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
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<td>Date and version identifier</td>
<td>393</td>
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<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>4-12, 416-421</td>
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<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
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<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
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<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
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<tr>
<td>Introduction</td>
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<tr>
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<td>6a</td>
<td>Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention</td>
<td>68-106</td>
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<tr>
<td></td>
<td>6b</td>
<td>Explanation for choice of comparators</td>
<td>110-112</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
<td>125-140</td>
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Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 142-145

Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained 148-149

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) 151-182

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 184-213

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) 215-222

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended 224-252

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Figure 2

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 254-262

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 264-267

Methods: Assignment of interventions (for controlled trials)

Allocation:
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation 399-403

Dissemination policy 31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions 408-412

31b Authorship eligibility guidelines and any intended use of professional writers

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials 32 Model consent form and other related documentation given to participants and authorised surrogates

Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.
**Emotional freedom technique versus written exposure therapy versus waiting list for post-traumatic stress disorder: protocol for a randomized clinical MRI study**

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| **Primary Subject Heading:** | Mental health |
| **Secondary Subject Heading:** | Complementary medicine |
| **Keywords:** | Anxiety disorders < PSYCHIATRY, Magnetic resonance imaging < RADIOTHERAPY, Clinical trials < THERAPEUTICS |
Emotional freedom technique versus written exposure therapy versus waiting list for post-traumatic stress disorder: protocol for a randomized clinical MRI study

Yujin Choi1,†, Yunna Kim2, 3,†, Sunyoung Choi1, Young-Eun Choi4, Ojin Kwon1, Do-Hyung Kwon2, 3, 5, Seung-Ho Lee2, 3, 5, Seung-Hun Cho2, 3, *, Hyungjun Kim1, *

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ABSTRACT

Introduction: The emotional freedom techniques (EFT) is an acupuncture-based psychotherapy that combines tapping on acupoints with cognitive reframing. EFT has been previously shown to have potential for treating post-traumatic stress disorder (PTSD). However, further clinical evidence and underlying mechanisms of EFT are yet to be fully explored. This proposed clinical trial aims to examine the effect of EFT on patients with PTSD compared with the waitlist (WL) and active controls.

Methods and analysis: This study was designed as a randomized, assessor-blinded, three-arm clinical MRI study. A total of 120 eligible patients with PTSD will be recruited and randomized into EFT, written exposure therapy (WET), or WL groups. EFT and WET will be applied once a week for 5 weeks. For patients in the WL group, EFT will be performed after 12 weeks. PTSD symptoms, depression, anxiety, somatic symptoms, and quality of life will be evaluated. Assessments will be conducted at baseline (week 0), post-treatment (week 6), and follow-up (week 12). Structural and functional brain images and recording videos of facial expressions to emotional stimuli will be obtained before and after treatment. Sixty participants without lifetime traumatic experiences will be enrolled as healthy controls. The primary objective of the study is to compare the change from baseline in the Clinician-Administered PTSD Scale after treatment (week 6) between EFT and WL groups and between EFT and WET groups.

Ethics and dissemination: Ethical approval was obtained from the Institutional Review Board of the Kyung Hee University Korean Medicine Hospital. The research findings will be shared at national and international conferences and will be published in peer-reviewed journals.

Trial registration number: Clinical Research Information Service: KCT0007360
https://cris.nih.go.kr/cris/search/detailSearch.do/21974

Keywords: Stress Disorders, Post-Traumatic; Emotional Freedom Techniques; Magnetic Resonance Imaging; Randomized Controlled Trial; Clinical Protocols
Strengths and limitations of this study

- This will be the first randomized controlled trial to evaluate the emotional freedom techniques for patients with post-traumatic stress disorder compared with the waitlist controls and written exposure therapy.
- This study will collect a wide range of data, including an assessment of clinical symptoms, questionnaires, recording videos of facial expressions to emotional stimuli, and structural and functional MRI, to investigate the underlying neurological mechanisms.
- Additionally, baseline characteristics and changes after treatment of patients with post-traumatic stress disorder will be examined in comparison with healthy controls without traumatic experiences.
- Because of the nature of psychotherapy interventions, blinding of participants and clinicians is not feasible. Only assessors will be blinded.
INTRODUCTION

Background and rationale

Post-traumatic stress disorder (PTSD) is a disorder that occurs after exposure to traumatic events such as death, serious injury, or sexual violence. These symptoms include repetitive and painful memories of the traumatic event, intrusive symptoms such as dreams, persistent avoidance of stimuli associated with the traumatic event, negative changes in cognition and emotion associated with the traumatic event, and pronounced arousal and responsiveness associated with the traumatic event. According to the 2021 National Mental Health Survey conducted in Korea, the lifetime prevalence of PTSD is 1.5% (1.3% for men, 1.6% for women), and the annual prevalence is 0.3% (0.2% for men, 0.3% for women). PTSD often involves depressive, substance use, and anxiety disorders simultaneously.

Trauma-focused psychotherapy is the first-line treatment for PTSD. Strongly recommended treatments for PTSD include cognitive-behavioral therapy, cognitive processing therapy, cognitive therapy, and prolonged exposure therapy. Among the various psychotherapies for PTSD, exposure therapy is one of the most studied and well-established treatments. However, trauma-focused exposure therapy has a high dropout rate. A meta-analysis reported that 36% of patients who received trauma-specific treatment dropped out in clinical trials, and a dropout rate of 30% in real-world practice in the United States Veterans Health Administration Prolonged Exposure Training Program was similar. Two major reasons why veterans dropped out of trauma-focused psychotherapy were a lack of buy-in to treatment and too stressful course, which were mostly related to uncomfortable exposure to the past. Thus, effective therapy with low drop-out rate is required in patients with PTSD.

The emotional freedom techniques (EFT) is a acupuncture-based psychotherapy that combines tapping on acupoints and exposure to cognitive reframing. Recently, a systematic review summarized that EFT treatment is effective for psychological and physiological conditions. In reviews on the effect of EFT on patients who experienced traumatic events and were at a high risk of PTSD, 4–10 EFT sessions were effective for PTSD symptoms and were proven to be safe. Two randomized controlled trials reported that EFT is potentially effective in improving PTSD symptoms in patients who are diagnosed as PTSD. Karatrias et al. reported that after 8 weeks of EFT treatment, PTSD symptom levels decreased and persisted after a 3-month follow-up, which was not significantly different from those of eye movement desensitization and reprocessing (EMDR) treatment. In another study, Church et al. reported that a 4-week EFT treatment reduced PTSD
symptom levels and psychological distress compared to the standard care wait list.\textsuperscript{16}

According to the assessment by the Korean Medicine Procedure Expert Assessment Committee on April 29, 2021, EFT using acupuncture point tapping was determined as a safe and non-invasive method for symptom improvement in PTSD compared to palliative treatment. However, it was pointed out that there is limited evidence and follow-up data of EFT in PTSD when compared with cognitive-behavioral therapy and EMDR, which are currently recommended as psychotherapies for the treatment of PTSD in textbooks and guidelines.\textsuperscript{17} The aforementioned randomized controlled trials have limitations in that both included a small number of participants (46 and 59, respectively) and used symptom-related parameters to assess efficacy.\textsuperscript{15,16} Therefore, further studies with a sufficient number of participants are necessary to examine the effectiveness of EFT in PTSD.

Before planning this trial, we conducted a feasibility trial of a 5-session EFT in 30 patients diagnosed with PTSD. In this before-and-after study, PTSD symptoms of participants generally improved after the EFT intervention, compliance with attending EFT sessions was high, and the dropout rate was low. In this trial, we selected written exposure therapy (WET)\textsuperscript{18,19} as an active control, as it is a short-term therapy that is adequate for comparison with 5-session of EFT. In addition, the waiting list was included as another control group, and this trial will be planned with a three-arm parallel design.

A critical limitation is that there are no well-established biomarkers related to either the diagnosis or prognosis of PTSD.\textsuperscript{20} Exploring the underlying mechanisms and seeking predictive factors for the response to PTSD treatments are also important, in addition to simply evaluating the efficacy of the treatment.\textsuperscript{21} To meet such demands, attempts have been made to identify biomarkers for PTSD using various methodologies.\textsuperscript{22} In comparison with non-trauma controls, patients with PTSD showed left amygdala hyperactivation, and in comparison with non-trauma controls and trauma-exposed controls, patients with PTSD exhibited diminished activation in the medial prefrontal cortex.\textsuperscript{23} In a longitudinal functional magnetic resonance imaging (fMRI) study, higher dorsal anterior cingulate cortex, insula, and amygdala activations in response to negative pictures was a predictor of poor response to PTSD treatment.\textsuperscript{21} In the present study, structural and functional brain images will be obtained before and after the intervention to explore the underlying mechanisms.

**Objectives**

The primary objectives are to evaluate the effect of EFT on PTSD symptoms compared to the waiting list (WL) and to evaluate the non-inferiority of EFT on PTSD symptoms compared to WET. The change from baseline in the Clinician-Administered PTSD Scale (CAPS-5) after the intervention will
be compared between the EFT and WL groups and between the EFT and WET groups.

The secondary objectives are to evaluate the effect of EFT compared to WL and WET based on the proportion of loss of PTSD diagnosis and full remission of PTSD after the intervention. Additionally, self-reported PTSD symptoms will be evaluated using the PTSD Checklist-5 (PCL-5), and depression and anxiety will be assessed using the Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI). Somatic symptoms and insomnia will be assessed using the Patient Health Questionnaire (PHQ)-15 and Insomnia Severity Index (ISI). Quality of life will also be evaluated using the EuroQol-5 Dimension-5 Levels (EQ-5D-5L) and World Health Organization quality of life assessment instrument abbreviated version (WHOQOL-BREF). Additionally, the compliance and drop-out rate of each group will be measured. The safety will be assessed through the incidence of adverse events and risk of suicide assessment.

The exploratory objectives are to investigate the biomarkers and predictors of PTSD diagnosis and prognosis, including (1) the detection of biomarkers for the diagnosis of PTSD at baseline compared to healthy controls, (2) the identification of predictors for individuals with a better prognosis among patients, and (3) understanding the underlying mechanisms of successful treatment. To achieve these objectives, potential biomarkers and predictors, including structural and functional MRI, recordings of facial expressions to emotional stimuli, and blood samples, will be collected longitudinally.

**Trial design**

This study is designed as a randomized, assessor-blinded, three-arm, parallel-group clinical MRI study. The 120 eligible patients with PTSD will be randomly allocated to the EFT, WET, or WL groups in a 1:1:1 ratio (Figure 1).

**METHODS AND ANALYSIS**

**Study setting**

This study will be conducted at a university hospital in Seoul, Korea.
Eligibility criteria

Patients with PTSD

The inclusion criteria of will be adults aged between 19 and 65 years; diagnosis of PTSD by Structured Clinical Interview for DSM-5 (SCID-5); symptoms of PTSD for >3 months, willing to attend weekly visits for 6 weeks; and patients who voluntarily agree to participate.

Exclusion criteria will be risk of suicide as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS); current or past history of schizophrenia or bipolar disorder; alcohol or other substance use disorders within 8 weeks; history of cerebrovascular diseases, brain tumor, or traumatic brain injury (participants with mild traumatic brain injury will not be excluded); history of neurological or systemic diseases that may affect the central nervous system; history of acute infectious disease within 2 weeks; history of taking the following medications within 4 weeks; use of systemic steroids, antipsychotics, antidepressants, benzodiazepines, sleep medications (participants taking the medications in stable doses for >2 weeks will not be excluded); history of taking antibiotics within 2 weeks; vaccination within 4 weeks or plans for vaccination during the study period; moderate or higher cognitive impairment; medical conditions requiring inpatient treatment; receipt of medication or other interventions in other clinical trials within 1 month; current active psychotherapy; pregnant or lactating women; women who do not use medically acceptable contraception during the study period; those determined as unsuitable by the investigators.

Healthy controls

The inclusion criteria for healthy controls will be adults aged between 19 and 65 years, those without traumatic experiences, those who do not meet the diagnostic criteria of PTSD according to the SCID-5, those who do not have functional/organic disorders and clinically meaningful findings in the history taking and physical examination, PHQ-9 score ≤4, Generalized Anxiety Disorder Screener-7 score ≤4, PHQ-15 score ≤5, and those who voluntarily agree to participate.

The exclusion criteria for healthy controls will include a history of major mental disorders. The other exclusion criteria are shown the clinical study registration. The baseline characteristics between PTSD patients and healthy controls will be compared, to explore the biomarkers of PTSD diagnosis. Healthy controls will be recruited in the same site, after the enrollment of patients with PTSD, with balanced sex and age.
MRI-specific exclusion criteria

These exclusion criteria will be applied to patients with PTSD and the healthy controls: ferrous-containing metal substance within the body and difficulty tolerating enclosed, small spaces because of claustrophobia.

Interventions

EFT

EFT consists of five, 40-minute, weekly sessions that include tapping on acupoints and exposure to cognitive reframing. The EFT protocol for patients with PTSD was developed on the basis of previous studies. In the previous feasibility trial, a developed EFT protocol was applied to 30 patients with PTSD in Korea, and the mean PCL-5 score was decreased to -14.33 (95% confidence interval [CI]: -19.79, -8.86) points after the five sessions of EFT. In the first session, the therapist will provide an introduction to EFT. In every session of EFT, therapists will follow the instructions from the EFT Manual (4th edition). At the beginning of each session, the patient and therapist will define the problem and evaluate the level of emotional distress. They will then create a "set-up statement," acknowledging the problem and accepting oneself while tapping the SI3 acupoint on the side of the hand. This is one of the essential parts of EFT and includes exposure to trauma with cognitive reframing, where the patient is encouraged to reframe their negative thoughts about the problem in a more positive light. The therapist will then conduct the first sequence of EFT tapping, tapping on various acupoints while repeating a brief phrase of the problem seven times. After this, the Gamut Procedure will be conducted, and the second sequence of EFT tapping will be repeated. The change in emotional distress will be re-evaluated after the sequences.

WET

WET consists of five, 40-minute, weekly sessions that focus on expressive writing about a traumatic event. We will follow the WET protocol developed by Sloan et al. This WET protocol was applied to patients with PTSD in Korea, and the severity of PTSD symptoms was alleviated with large effect size (partial $\eta^2$: 0.524 for PCL-5) after five sessions of WET. In the first session, therapists will introduce WET and select the trauma experience to be covered in this WET session. Before writing, the subjective units of distress (between 0 and 100) will be checked. Instructions for writing will be provided using the WET script developed by Sloan et al., which ensure the standard delivery of WET protocol, and participants will write about their trauma in detail for 30 minutes. From the
second to the fifth sessions, specific writing instructions will be provided using the WET script, and 30 minutes of the writing session will be completed. EFT and WET will be applied by qualified therapists working at the Department of Neuropsychiatry in Korean medicine, who have completed exposure-based treatment and Clinical EFT or WET protocol training. The treatment fidelity will be monitored by the perusal of the therapist written notes by investigators to ensure that all Clinical EFT and WET standards are met. In addition, to improve adherence to the intervention, participants will be encouraged to visit at predetermined times through regular phone and text messages.

WL

The participants assigned to WL will not receive any intervention until completion of the follow-up visit. After 12 weeks, the follow-up visit and evaluation will be completed, and EFT will be applied to participants in the WL group. For all participants in the three groups, the use of systemic steroids, antipsychotics, antidepressants, benzodiazepines, and sleep medications that were not used at the time of enrollment will be prohibited. If any of these medications are newly administered after enrollment, the participant will be excluded from the per protocol set. However, other medications that were administered four weeks before study enrollment, as well as transient medications for other diseases or symptoms, may be allowed at the clinical discretion of the investigators, provided that those medications are not expected to significantly affect the study results.

Criteria for discontinuing or modifying allocated interventions

Participants will be considered for treatment cessation and elimination from the study if they meet following criteria: participants who found to be not meeting the inclusion and exclusion criteria, participants with serious adverse events (death, life-threatening, or hospitalization due to adverse events), participants with adverse events warranting discontinuation of the study intervention, participants with symptom aggravation and in need of another treatment, participants who withdraw consent, participants who are lost to follow-up, and participants who are unsuitable for continuing administration by the investigators.
Outcomes

Primary outcome

The primary outcome is the mean change from the baseline CAPS-5 score at week 6 (post-treatment). CAPS-5 is a representative clinician rating scale for PTSD. The CAPS-5 score will be measured at baseline, week 6 (post-treatment), and week 12 (follow-up). The mean change in CAPS-5 scores between baseline and week 6 will be the primary outcome.

Secondary outcomes

The mean change from the baseline CAPS-5 score at week 12 (follow-up), loss of PTSD diagnosis, and full remission rates at week 6 (post-treatment) and week 12 (follow-up) will be secondary outcomes used to assess the severity of PTSD symptoms. Loss of PTSD diagnosis and full remission of PTSD will be defined based on the results of CAPS-5. Loss of PTSD diagnosis will be defined as no longer meeting the diagnostic criteria for PTSD, which includes experiencing fewer than the required number of symptoms in each criterion. A total CAPS-5 score <20 will be defined as the remission of PTSD. Additionally, PCL-5 will be used as a self-rating scale to assess the severity of PTSD symptoms. BDI-II and BAI will be used to assess the severity of depression and anxiety symptoms, respectively. Additionally, PHQ-15 and the Insomnia Severity Index (ISI) will be used to assess the severity of somatic symptoms in patients with PTSD. To evaluate the quality of life in patients with PTSD, EQ-5D-5L and WHOQOL-BREF scores will be used as secondary outcomes.

Safety outcomes

The incidence of adverse events will be presented in three groups based on severity and causality assessment. The occurrence of adverse events will be monitored at every visit. Additionally, the risk of suicide will be evaluated by the investigators using C-SSRS at screening, week 6 (post-treatment), and week 12 (follow-up).

Exploratory outcomes

Exploratory outcomes will be measured before and after the intervention (weeks 0 and 6). Structural and functional brain images will be obtained using 3T MRI. Emotional tasks that induce emotions of joy, anxiety, and sadness by watching video clips will be conducted, and the facial expressions of participants during the tasks will be recorded. The facial expression analysis.
will be conducted using iMotions software. In addition, empathy quotient,\textsuperscript{46-48} and irritable bowel severity symptom severity scale\textsuperscript{49} will be measured as exploratory outcomes. Figure 2 summarize the participant timeline.

**Sample size**

The sample size was computed to detect the mean difference in change from the baseline CAPS-5 score after treatment between the EFT and WL groups. No previous study has compared the CAPS-5 scores between EFT and WL. We estimated that EFT would have an effect size similar to that of EMDR,\textsuperscript{15} and in a previous study comparing EMDR with WL, the effect size (Cohen $\delta$) of EMDR was 0.65.\textsuperscript{50} With a two-sided significance level of 0.05 and a power of 0.8, 38.14 participants are required in each group. Considering a dropout rate of 5%, 40 participants will be recruited per group, and a total of 120 will be investigated. The dropout rate was calculated based on a previous feasibility trial of EFT in patients with PTSD.

**Recruitment**

To achieve adequate participant recruitment, regular advertisements will be conducted through online media, and approved materials will be attached to the bulletin boards inside and outside of the hospital. In the case of delayed recruitment, local advertisement can be implemented. The first participant of the study was enrolled on December 8th, 2022, and the date of the last observation is expected to be completed in December 2025.

**Allocation**

Random assignment will be performed in compliance with group assignments that are not biased and not exposed to participants and researchers. An independent statistician who is not involved in the performance and evaluation of this clinical trial generated a random assignment sequence in a 1:1:1 ratio for each group using blocked randomization in SAS\textsuperscript{®} (version 9.4, SAS Institute Inc., Cary, NC, USA). The generated random sequence table will be kept by the independent statistician and protected from disclosure.

For each random number, the assignment results will be sealed in an opaque envelope and stored in a locked cabinet. Participants’ random numbers will be assigned according to the order in which the participants are enrolled at visit 2 after the screening process. A random number will be given
independently of the screening number. The corresponding envelope will be opened according to
the random number, and group assignment will be performed. The date and time of opening and
the signature of the researcher who opened it will be written on the open envelope and stored
separately.

### Blinding

The participants will be allocated to the EFT, WET, or WL groups, and it is impossible to blind
therapists and participants during the intervention. Nevertheless, this study is designed as an
assessor-blinded trial to control for bias as much as possible. Effectiveness and risk of suicide will
be evaluated by independent assessors who have not performed the intervention procedure or
random assignment. Visits for interventions (3–7) and assessment (2, 8, and 9) will be separated.

### Data collection methods

To assess the severity of PTSD symptoms, the CAPS-5 (clinician-administered tool) and PCL-5 (self-
reported instrument) will be used. The CAPS-5 consists of 30 items measuring the severity of PTSD
symptoms, and the total score ranges from 0 to 80, with higher scores indicating more severe
symptoms. The validated Korean version of the CAPS-5 will be used. CAPS-5 will be evaluated
by qualified investigators. To ensure the consistency of CAPS-5, an investigator meeting was
conducted for training before study initiation. The PCL-5 consists of 20 items measuring the severity
of PTSD symptoms in the DSM-5, and the total PCL-5 score ranges from 0 to 80, with higher scores
indicating severe symptoms. The validated Korean version of the PCL-5 will be used. To assess
PTSD and depressive symptoms during the intervention period, the PCL-5 and BDI-II will be
measured every 2 weeks. The BDI-II consists of 21 items, and the total score ranges from 0 to 63,
with higher scores indicating more severe symptoms. A validated Korean version of the BDI-II will
be used. Even if a participant withdraws consent, efforts will be made to schedule an evaluation
visit for the CAPS-5.

### Data management

Data in source documents (assessment sheets completed by investigators, questionnaires filled out
by participants, and electronic medical records) will be entered into the electronic Case Report Form
e(CRF). The eCRF was developed using the iCREaT (internet-based Clinical Research and Trial) system
provided by the Korea National Institute of Health. A data management plan was prepared before
study initiation. Data specifications were defined and source documents for each data point were agreed upon. Investigators at the institute were trained for data entry and coding using the eCRF system. The data entered in the eCRF will be checked bimonthly after enrolment of the first participant.

**Statistical methods**

**Analysis sets**

The analysis sets will be defined as follows. 1) Full analysis (FA) set: Population that complies with the intention-to-treat principle, meets major inclusion and exclusion criteria, and has obtained at least one primary outcome assessment after the baseline assessment. 2) Per protocol set: Population within the FA set who have ≥80% compliance with the interventions, do not take any prohibited medications, and do not have major violations to the protocol. 3) Safety analysis set: Population consisting of all participants whose safety assessment has been made at least once since the randomized allocation.

**Statistical methods for analyzing the primary outcome**

This is a multi-arm parallel-group randomized trial, and there are three hypotheses for the primary outcome. The first null hypothesis is that the mean change from baseline at week 6 in the EFT group will be the same as that in the WL group ($H_0 : \mu_1 = \mu_2$, $H_1 : \mu_1 \neq \mu_2$). A mixed-effect model repeated measure (MMRM) will be used, with group and time as fixed factors, and participant as a random factor. The mean difference and 95% CI between two groups and p-values will be presented. The first hypothesis aims to assess the effect size of EFT on PTSD symptoms compared with WL.

The second null hypothesis is that the mean change from baseline at week 6 in the WET group will be the same as that in the WL group ($H_0 : \mu_3 = \mu_2$, $H_1 : \mu_3 \neq \mu_2$). MMRM will be used as in the first hypothesis. From the results of the second hypothesis, the non-inferiority margin (M) will be defined. The lower limit of the 95% CI of the mean difference between two groups will be M.

The third null hypothesis is that the mean change from the baseline at week 6 in the WET and EFT group will be greater than M ($H_0 : \mu_3 - \mu_1 > M$, $H_1 : \mu_3 - \mu_1 \leq M$). The third hypothesis assesses the non-inferiority of EFT compared with WET, and M calculated in the second hypothesis will be used. MMRM will be used, similar to the first hypothesis, but the significance level will be set to 2.5% since the non-inferiority test is one-sided.
The problem of multiple testing will be solved using the fixed sequence method. If the statistical result for hypothesis 1 is significant, the tests for hypotheses 2 and 3 will be performed. If the first null hypothesis were not rejected, tests for hypotheses 2 and 3 will not be performed. If the first null hypothesis is rejected and the test for hypothesis 2 is performed, in case that the statistical result for hypothesis 2 is significant, the test for hypothesis 3 will be conducted.

Statistical methods for analyzing the secondary outcomes

Continuous variables (mean changes in CAPS-5, PCL-5, BDI-II, BAI, PHQ-15, ISI, EQ-5D-5L, WHOQOL-BREF, and Clinical Global Impression scores) will be tested using the same method as for the primary outcome. Additionally, to compare the difference between before and after the intervention in each group, the Student paired t-test or Wilcoxon signed-rank test will be used. Repeated measures analysis of variance will be performed to test the interaction between group and time.

Binary variables (loss of PTSD diagnosis and full remission of PTSD) will be tested using logistic regression analysis. Odds ratios (95% CI) for the two groups will be presented. Hypothesis setting and multiple-testing problem-solving methods will be the same as those used for the primary outcome.

Statistical methods used to handle missing data

The primary outcome will be analyzed using MMRM. The MMRM considers missing data using the maximum likelihood, and does not require the process of replacing the missing data. In the case of an additional analysis of covariance, missing data will be replaced using the multiple imputation method.

Data monitoring

Considering the low risk of interventions and the study purpose, a data monitoring committee is not needed. An interim analysis is not planned. If intervention-related moderate or severe adverse events occur in >25% of all participants, the study will be stopped.
Harms

Adverse events will be carefully recorded at every visit, and the frequency, severity, and causality of the adverse events will be assessed in the three groups. Additionally, the suicide risk of the participants will be evaluated using the Columbia Suicide Severity Rating Scale.

Auditing

Monitoring will be conducted to verify that the clinical study data are accurate and complete, and that the clinical study is performed in accordance with the approved protocol and related regulations. Monitoring of clinical studies will be conducted through regular visits to the institute. The scope of monitoring will include compliance with the clinical study protocol, collection of appropriate and accurate data, obtaining informed consent, and recording adverse events. The monitor will check the eCRF, source documents, and essential documents during regular visits.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

Research ethics approval

This study has been approved by the Institutional Review Board (IRB) of the Kyung Hee University Korean Medicine Hospital (KOMCIRB2021-11-005-001).

Protocol amendments

Protocol modifications will be determined after sufficient discussion by investigators at the hospital and KIOM and will be applied to the study after obtaining approval for the amendment from the IRB. The current version of protocol is 1.7 (date: 2023-03-28).
**Consent or assent**

Written informed consent will be obtained from all participants prior to screening. The principal investigator and sub-investigators, who are Korean medicine doctors in the hospital and delegated by the principal investigator, will provide information about the clinical study and obtain informed consent from the participants. Informed consent and a description of the study approved by the IRB will be used. Sufficient time and opportunity for the participants to ask questions about the details of the clinical study and to decide whether to participate will be provided. Additional consent will be obtained for the collection and analysis of blood samples.

**Confidentiality**

The personal information of each participant will not be entered into eCRF, and the data of each participant will be collected under screening and random numbers.

**Ancillary and post-trial care**

Follow-up observation and online follow-up observation will be conducted at weeks 12 and 24. Compensation criteria and plans will be prepared for those who suffer harm from trial participation. The occurrence of adverse events will be assessed at every visit, and the required treatment and observation will be applied until the symptoms disappear.

**Dissemination policy**

The clinical study information and results will be registered with the Clinical Research Information Service. This study’s findings will be presented at conferences and published in peer-reviewed journals. The participant-level dataset will be uploaded to the Korean Medicine Data Repository (kmdr.kiom.re.kr) after study completion.
**Author contributions**

H Kim, SH Cho, Y Choi, Y Kim, and S Choi conceived the trial. YE Choi, O Kwon, D Kwon, and S Lee helped with study implementation. Y Choi and Y Kim completed the initial draft of the manuscript. O Kwon generated the randomization sequence and provided biostatistical advice and information. All authors designed the study and read, edited, and approved the final manuscript and supplementary files.

**Funding**

This work was supported by the Korea Institute of Oriental Medicine (KIOM) (grant number: KSN2211010). As a government-funded research institute, KIOM is responsible for the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

**Competing interests**

None declared.

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Hyungjun Kim, https://orcid.org/0000-0001-7997-7663
References


29. Weathers FW, Blake DD, Schnurr PP, Kaloupek D, Marx BP, Keane TM. *The clinician-
administrated PTSD scale for DSM-5 (CAPS-5). National Center for PTSD; 2013.


**Figure legends**

**Figure 1** Flow diagram.

LEC-5, Life Event Checklist for DSM-5; CTQ, Childhood Trauma Questionnaire; SCID-5, Structured Clinical Interview for DSM-5; C-SSRS, Columbia Suicide Severity Rating Scale; CAPS-5, Clinician-Administered PTSD Scale; CGI-S, Clinical Global Impressions-Severity scale; CGI-I, Clinical Global Impressions-Improvement scale; PCL-5, PTSD Checklist-5; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Index; PHQ-15, Patient Health Questionnaire-15; ISI, Insomnia Severity Index; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; WHOQOL-BREF, WHO QoL assessment instrument abbreviated version; EQ, empathy Quotient; IBS-SSS, Irritable Bowel Symptoms Severity Scale.

**Figure 2** The schedule of enrolment, intervention and assessment.

1 The participants assigned to WL will not receive any intervention until completion of the follow-up visit. After 12 weeks, EFT will be applied to participants in the WL group.

2 The facial expressions will be recorded during the emotional task.

EFT, Emotional Freedom Technique; WET, Written Exposure Therapy; WL, Waiting List; CAPS-5, Clinician-Administered PTSD Scale; CGI-S, Clinical Global Impressions-Severity scale; CGI-I, Clinical Global Impressions-Improvement scale; PCL-5, PTSD Checklist-5; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Index; PHQ-15, Patient Health Questionnaire-15; ISI, Insomnia Severity Index; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; WHOQOL-BREF, WHO QoL assessment instrument abbreviated version; EQ, empathy Quotient; IBS-SSS, Irritable Bowel Symptoms Severity Scale.
Visit 1
Screening
~2weeks

Screening: Informed consent, Demographics, Medical history, Physical examination, Blood test, LEC-5, CTQ, SCID-5, C-SSRS, Eligibility assessment

Visit 2
Baseline
Week 0

Total N: 120

Visit 3-7
Intervention
Week 1-5

Randomization
EFT
N=40

WET
N=40

WL
N=40

EFT or WET (Visit 3-7), PCL-5, BDI-II (Visit 4, 6)

Visit 8
Post-treatment
Week 6


Visit 9
Follow-up
Week 12


Visit 10
Close-out
Week 24

<table>
<thead>
<tr>
<th>Time point</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Intervention</th>
<th>Assessment</th>
<th>Follow-up</th>
<th>Close-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ -14 days</td>
<td>Visit 1</td>
<td>Visit 2</td>
<td>Visit 3 ~ Visit 7</td>
<td>Visit 8</td>
<td>Visit 9</td>
<td>Visit 10</td>
</tr>
</tbody>
</table>

**ENROLMENT:**
- Informed consent X
- Eligibility screen X
- C-SSRS X X
- Allocation X

**INTERVENTIONS:**
- EFT X X X X X
- WET X X X X X
- WL

**ASSESSMENTS:**
- CAPS-5 X X
- CGI-S X X
- CGI-I X
- PCL-5, BDI-II X X X X X
- BAI X X X
- PHQ-15, ISI X X X
- EQ-5D-5L, WHOQOL-BREF X X X
- MRI X
- Emotional task X
- EQ, IBS-SSS X X

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
# SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

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<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
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</thead>
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<tr>
<td>Administrative information</td>
<td></td>
<td></td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
<td>1-3</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
<td>48-49</td>
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<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
<td>49 (URL)</td>
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<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
<td>430</td>
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<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
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<tr>
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<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
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<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
<td>465-467</td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Introduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background and rationale</td>
<td>6a</td>
<td>Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention</td>
<td>67-107</td>
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<tr>
<td></td>
<td>6b</td>
<td>Explanation for choice of comparators</td>
<td>111-113</td>
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<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
<td>126-147</td>
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</table>
Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 149-152

Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained 155-156

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) 158-192

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 194-239

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) 241-248

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 226-227

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 232-239

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended 250-284

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) 286-301

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 286-294

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 296-301

Methods: Assignment of interventions (for controlled trials)

Allocation:
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<th>Details</th>
<th>Pages</th>
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</thead>
<tbody>
<tr>
<td>Sequence generation 16a</td>
<td>Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.</td>
<td>304-309</td>
</tr>
<tr>
<td>Allocation concealment mechanism 16b</td>
<td>Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.</td>
<td>310-316</td>
</tr>
<tr>
<td>Implementation 16c</td>
<td>Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.</td>
<td>304-316</td>
</tr>
<tr>
<td>Blinding (masking) 17a</td>
<td>Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how.</td>
<td>318-323</td>
</tr>
<tr>
<td>17b</td>
<td>If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial.</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**Methods: Data collection, management, and analysis**

| Data collection methods 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol. | 325-337 |
| 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols. | 337-338 |
| Data management 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol. | 340-348 |
| Statistical methods 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. | 360-392 |
| 20b | Methods for any additional analyses (e.g., subgroup and adjusted analyses). | 396-398 |
Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring

Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval

Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments

Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent

Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality

How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests

Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data

Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
<table>
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<th>Section</th>
<th>Number</th>
<th>Description</th>
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<td>Ancillary and</td>
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<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
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<tr>
<td>Dissemination policy</td>
<td>31a</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
<td>465-469</td>
</tr>
<tr>
<td></td>
<td>31b</td>
<td>Authorship eligibility guidelines and any intended use of professional writers.</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
<td>468-469</td>
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**Appendices**

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<td>Biological specimens</td>
<td>33</td>
<td>Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable</td>
<td>452-453</td>
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</table>

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyright by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.*
Emotional freedom techniques versus written exposure therapy versus waiting list for post-traumatic stress disorder: protocol for a randomized clinical MRI study

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<th>BMJ Open</th>
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<td>Protocol</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>26-May-2023</td>
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| Complete List of Authors: | Choi, Yujin; Korea Institute of Oriental Medicine, KM Science Research Division  
Kim, Yunna; Kyung Hee University, Department of Neuropsychiatry, College of Korean Medicine, Kyung Hee University Medical Center; Kyung Hee University, Research group of Neuroscience, East-West Medical Research Institute, WHO Collaborating Center  
Choi, Sunyoung; Korea Institute of Oriental Medicine, KM Science Research Division  
Choi, Young Eun; Korea Institute of Oriental Medicine  
Kwon, O-Jin; Korea Institute of Oriental Medicine, KM Science Research Division  
Kwon, Dohyeong; Kyung Hee University, Department of Neuropsychiatry, College of Korean Medicine, Kyung Hee University Medical Center; Kyung Hee University, Research group of Neuroscience, East-West Medical Research Institute, WHO Collaborating Center  
Lee, Seung-Ho; Kyung Hee University, Department of Neuropsychiatry, College of Korean Medicine, Kyung Hee University Medical Center; Kyung Hee University, Research group of Neuroscience, East-West Medical Research Institute, WHO Collaborating Center  
Cho, Seung-Hun; Kyung Hee University, Department of Neuropsychiatry, College of Korean Medicine, Kyung Hee University Medical Center; Kyung Hee University, Research group of Neuroscience, East-West Medical Research Institute, WHO Collaborating Center  
Kim, Hyungjun; Korea Institute of Oriental Medicine, KM Science Research Division |
| Primary Subject Heading: | Mental health |
| Secondary Subject Heading: | Complementary medicine |
| Keywords: | Anxiety disorders < PSYCHIATRY, Magnetic resonance imaging < RADIOTHERAPY, Clinical trials < THERAPEUTICS |
Emotional freedom techniques versus written exposure therapy versus waiting list for post-traumatic stress disorder: protocol for a randomized clinical MRI study

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ABSTRACT

Introduction: The emotional freedom techniques (EFT) is an acupuncture-based psychotherapy that combines tapping on acupoints with cognitive reframing. EFT has been previously shown to have potential for treating post-traumatic stress disorder (PTSD). However, further clinical evidence and underlying mechanisms of EFT are yet to be fully explored. This proposed clinical trial aims to examine the effect of EFT on patients with PTSD compared with the waitlist (WL) and active controls.

Methods and analysis: This study was designed as a randomized, assessor-blinded, three-arm clinical MRI study. A total of 120 eligible patients with PTSD will be recruited and randomized into EFT, written exposure therapy (WET), or WL groups. EFT and WET will be applied once a week for 5 weeks. For patients in the WL group, EFT will be performed after 12 weeks. PTSD symptoms, depression, anxiety, somatic symptoms, and quality of life will be evaluated. Assessments will be conducted at baseline (week 0), post-treatment (week 6), and follow-up (week 12). Structural and functional brain images and recording videos of facial expressions to emotional stimuli will be obtained before and after treatment. Sixty participants without lifetime traumatic experiences will be enrolled as healthy controls. The primary objective of the study is to compare the change from baseline in the Clinician-Administered PTSD Scale after treatment (week 6) between EFT and WL groups and between EFT and WET groups.

Ethics and dissemination: Ethical approval was obtained from the Institutional Review Board of the Kyung Hee University Korean Medicine Hospital. The research findings will be shared at national and international conferences and will be published in peer-reviewed journals.


Keywords: Stress Disorders, Post-Traumatic; Emotional Freedom Techniques; Magnetic Resonance Imaging; Randomized Controlled Trial; Clinical Protocols
Strengths and limitations of this study

- This will be the first randomized controlled trial to evaluate the emotional freedom techniques for patients with post-traumatic stress disorder compared with the waitlist controls and written exposure therapy.
- This study will collect a wide range of data, including an assessment of clinical symptoms, questionnaires, recording videos of facial expressions to emotional stimuli, and structural and functional MRI, to investigate the underlying neurological mechanisms.
- Additionally, baseline characteristics and changes after treatment of patients with post-traumatic stress disorder will be examined in comparison with healthy controls without traumatic experiences.
- Because of the nature of psychotherapy interventions, blinding of participants and clinicians is not feasible. Only assessors will be blinded.
INTRODUCTION

Background and rationale

Post-traumatic stress disorder (PTSD) is a disorder that occurs after exposure to traumatic events such as death, serious injury, or sexual violence. These symptoms include repetitive and painful memories of the traumatic event, intrusive symptoms such as dreams, persistent avoidance of stimuli associated with the traumatic event, negative changes in cognition and emotion associated with the traumatic event, and pronounced arousal and responsiveness associated with the traumatic event.\(^1\) According to the 2021 National Mental Health Survey conducted in Korea, the lifetime prevalence of PTSD is 1.5% (1.3% for men, 1.6% for women), and the annual prevalence is 0.3% (0.2% for men, 0.3% for women).\(^2\) PTSD often involves depressive, substance use, and anxiety disorders simultaneously.\(^3\)

Trauma-focused psychotherapy is the first-line treatment for PTSD.\(^4,5\) Strongly recommended treatments for PTSD include cognitive-behavioral therapy, cognitive processing therapy, cognitive therapy, and prolonged exposure therapy.\(^6\) Among the various psychotherapies for PTSD, exposure therapy is one of the most studied and well-established treatments.\(^7\) However, trauma-focused exposure therapy has a high dropout rate. A meta-analysis reported that 36% of patients who received trauma-specific treatment dropped out in clinical trials, and a dropout rate of 30% in real-world practice in the United States Veterans Health Administration Prolonged Exposure Training Program was similar.\(^8,9\) Two major reasons why veterans dropped out of trauma-focused psychotherapy were a lack of buy-in to treatment and too stressful course, which were mostly related to uncomfortable exposure to the past.\(^10\) Thus, effective therapy with low drop-out rate is required in patients with PTSD.

The emotional freedom techniques (EFT) is a acupuncture-based psychotherapy that combines tapping on acupoints and exposure to cognitive reframing.\(^11\) Recently, a systematic review summarized that EFT treatment is effective for psychological and physiological conditions.\(^12\) In reviews on the effect of EFT on patients who experienced traumatic events and were at a high risk of PTSD, 4–10 EFT sessions were effective for PTSD symptoms and were proven to be safe.\(^13,14\) Two randomized controlled trials reported that EFT is potentially effective in improving PTSD symptoms in patients who are diagnosed as PTSD.\(^15,16\) Karatrias et al. reported that after 8 weeks of EFT treatment, PTSD symptom levels decreased and persisted after a 3-month follow-up, which was not significantly different from those of eye movement desensitization and reprocessing (EMDR) treatment.\(^15\) In another study, Church et al. reported that a 4-week EFT treatment reduced PTSD
symptom levels and psychological distress compared to the standard care wait list.\(^{16}\)

According to the assessment by the Korean Medicine Procedure Expert Assessment Committee on April 29, 2021, EFT using acupuncture point tapping was determined as a safe and non-invasive method for symptom improvement in PTSD compared to palliative treatment. However, it was pointed out that there is limited evidence and follow-up data of EFT in PTSD when compared with cognitive-behavioral therapy and EMDR, which are currently recommended as psychotherapies for the treatment of PTSD in textbooks and guidelines.\(^{17}\) The aforementioned randomized controlled trials have limitations in that both included a small number of participants (46 and 59, respectively) and used symptom-related parameters to assess efficacy.\(^{15,16}\) Therefore, further studies with a sufficient number of participants are necessary to examine the effectiveness of EFT in PTSD.

Before planning this trial, we conducted a feasibility trial of a 5-session EFT in 30 patients diagnosed with PTSD. In this before-and-after study, PTSD symptoms of participants generally improved after the EFT intervention, compliance with attending EFT sessions was high, and the dropout rate was low. In this trial, we selected written exposure therapy (WET)\(^{18,19}\) as an active control, as it is a short-term therapy that is adequate for comparison with 5-session of EFT. In addition, the waiting list was included as another control group, and this trial will be planned with a three-arm parallel design.

A critical limitation is that there are no well-established biomarkers related to either the diagnosis or prognosis of PTSD.\(^{20}\) Exploring the underlying mechanisms and seeking predictive factors for the response to PTSD treatments are also important, in addition to simply evaluating the efficacy of the treatment.\(^{21}\) To meet such demands, attempts have been made to identify biomarkers for PTSD using various methodologies.\(^{22}\) In comparison with non-trauma controls, patients with PTSD showed left amygdala hyperactivation, and in comparison with non-trauma controls and trauma-exposed controls, patients with PTSD exhibited diminished activation in the medial prefrontal cortex.\(^{23}\) In a longitudinal functional magnetic resonance imaging (fMRI) study, higher dorsal anterior cingulate cortex, insula, and amygdala activations in response to negative pictures was a predictor of poor response to PTSD treatment.\(^{21}\) In the present study, structural and functional brain images will be obtained before and after the intervention to explore the underlying mechanisms.

**Objectives**

The primary objectives are to evaluate the effect of EFT on PTSD symptoms compared to the waiting list (WL) and to evaluate the non-inferiority of EFT on PTSD symptoms compared to WET. The change from baseline in the Clinician-Administered PTSD Scale (CAPS-5) after the intervention will
be compared between the EFT and WL groups and between the EFT and WET groups.

The secondary objectives are to evaluate the effect of EFT compared to WL and WET based on the proportion of participants achieving criteria-based remission of PTSD and symptom-based remission of PTSD after the intervention. Additionally, self-reported PTSD symptoms will be evaluated using the PTSD Checklist-5 (PCL-5), and depression and anxiety will be assessed using the Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI). Somatic symptoms and insomnia will be assessed using the Patient Health Questionnaire (PHQ)-15 and Insomnia Severity Index (ISI). Quality of life will also be evaluated using the EuroQol-5 Dimension-5 Levels (EQ-5D-5L) and World Health Organization quality of life assessment instrument abbreviated version (WHOQOL-BREF). Additionally, the compliance and drop-out rate of each group will be measured. The safety will be assessed through the incidence of adverse events and assessment of suicide risk.

The exploratory objectives are to investigate the biomarkers and other predictors of PTSD diagnosis and prognosis, including (1) the detection of biomarkers for the diagnosis of PTSD at baseline compared to healthy controls, (2) the identification of biomarkers and other predictors for individuals with a better prognosis among patients, and (3) understanding the underlying mechanisms of successful treatment. To achieve these objectives, potential biomarkers and other predictors, including structural and functional MRI, recordings of facial expressions to emotional stimuli, and blood samples, will be collected longitudinally.

**Trial design**

This study is designed as a randomized, assessor-blinded, three-arm, parallel-group clinical MRI study. The 120 eligible patients with PTSD will be randomly allocated to the EFT, WET, or WL groups in a 1:1:1 ratio (Figure 1).

**METHODS AND ANALYSIS**

**Study setting**

This study will be conducted at a university hospital in Seoul, Korea.
Eligibility criteria

Patients with PTSD

The inclusion criteria of will be adults aged between 19 and 65 years; diagnosis of PTSD by Structured Clinical Interview for DSM-5 (SCID-5); symptoms of PTSD for >3 months, willing to attend weekly visits for 6 weeks; and patients who voluntarily agree to participate.

Exclusion criteria will be risk of suicide as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS); current or past history of schizophrenia or bipolar disorder; alcohol or other substance use disorders within 8 weeks; history of cerebrovascular diseases, brain tumor, or traumatic brain injury (participants with mild traumatic brain injury will not be excluded); history of neurological or systemic diseases that may affect the central nervous system; history of acute infectious disease within 2 weeks; history of taking the following medications within 4 weeks; use of systemic steroids, antipsychotics, antidepressants, benzodiazepines, sleep medications (participants taking the medications in stable doses for >2 weeks will not be excluded); history of taking antibiotics within 2 weeks; vaccination within 4 weeks or plans for vaccination during the study period; moderate or higher cognitive impairment; medical conditions requiring inpatient treatment; receipt of medication or other interventions in other clinical trials within 1 month; current active psychotherapy (based on early observation that a significant number of participants with PTSD had recently undergone psychotherapy, making it challenging to enroll participants with the original exclusion criteria of psychotherapy within 6 months, it was modified starting from protocol version 1.7. The characteristics of previously received psychotherapy will be carefully recorded and summarized as part of the baseline characteristics of enrolled participants.); pregnant or lactating women; women who do not use medically acceptable contraception (barrier methods, combined oral contraceptives, contraceptive implant, contraceptive injection, intrauterine devices, and personal or partner’s sterilization) during the study period; and those determined as unsuitable by the investigators.

Healthy controls

The inclusion criteria for healthy controls will be adults aged between 19 and 65 years, those without traumatic experiences, those who do not meet the diagnostic criteria of PTSD according to the SCID-5, those who do not have functional/organic disorders and clinically meaningful findings in the history taking and physical examination, PHQ-9 score ≤4, Generalized Anxiety Disorder Screener-7 score ≤4, PHQ-15 score ≤5, and those who voluntarily agree to participate.

The exclusion criteria for healthy controls will include a history of major mental disorders. The other exclusion criteria are shown the clinical study registration. The baseline characteristics between PTSD
191 patients and healthy controls will be compared, to explore the biomarkers of PTSD diagnosis.
192 Healthy controls will be recruited in the same site, after the enrollment of patients with PTSD, with balanced sex and age.

195 MRI-specific exclusion criteria
196 These exclusion criteria will be applied to patients with PTSD and the healthy controls: ferrous-containing metal substance within the body and difficulty tolerating enclosed, small spaces because of claustrophobia.

200 Interventions
201 EFT
202 EFT consists of five, 40-minute, weekly sessions that include tapping on acupoints and exposure to cognitive reframing. The EFT protocol for patients with PTSD was developed on the basis of previous studies. In the previous feasibility trial, a developed EFT protocol was applied to 30 patients with PTSD in Korea, and the mean PCL-5 score was decreased to -14.33 (95% confidence interval [CI]: -19.79, -8.86) points after the five sessions of EFT. In the first session, the therapist will provide an introduction to EFT. In every session of EFT, therapists will follow the instructions from the EFT Manual (4th edition). At the beginning of each session, the patient and therapist will define the problem and evaluate the level of emotional distress. They will then create a "set-up statement," acknowledging the problem and accepting oneself while tapping the SI3 acupoint on the side of the hand. This is one of the essential parts of EFT and includes exposure to trauma with cognitive reframing, where the patient is encouraged to reframe their negative thoughts about the problem in a more positive light. The therapist will then conduct the first sequence of EFT tapping, tapping on various acupoints while repeating a brief phrase of the problem seven times. After this, the 9 Gamut Procedure will be conducted, and the second sequence of EFT tapping will be repeated. The change in emotional distress will be re-evaluated after the sequences.

208 WET
209 WET consists of five, 40-minute, weekly sessions that focus on expressive writing about a traumatic event. We will follow the WET protocol developed by Sloan et al. This WET protocol was applied to patients with PTSD in Korea, and the severity of PTSD symptoms was alleviated with large effect.
size (partial $\eta^2$: 0.524 for PCL-5) after five sessions of WET. In the first session, therapists will introduce WET and select the trauma experience to be covered in this WET session. Before writing, the subjective units of distress (between 0 and 100) will be checked. Instructions for writing will be provided using the WET script developed by Sloan et al., which ensure the standard delivery of WET protocol, and participants will write about their trauma in detail for 30 minutes. From the second to the fifth sessions, specific writing instructions will be provided using the WET script, and 30 minutes of the writing session will be completed. EFT and WET will be applied by qualified therapists working at the Department of Neuropsychiatry in Korean medicine, who have completed exposure-based treatment and Clinical EFT or WET protocol training. The treatment fidelity will be monitored by the perusal of the therapist written notes by investigators to ensure that all Clinical EFT and WET standards are met. In addition, to improve adherence to the intervention, participants will be encouraged to visit at predetermined times through regular phone and text messages.

**WL**

The participants assigned to WL will not receive any intervention until completion of the follow-up visit. After 12 weeks, the follow-up visit and evaluation will be completed, and EFT will be applied to participants in the WL group. For all participants in the three groups, the use of systemic steroids, antipsychotics, antidepressants, benzodiazepines, and sleep medications that were not used at the time of enrollment will be prohibited. If any of these medications are newly administered after enrollment, the participant will be excluded from the per protocol set. However, other medications that were administered four weeks before study enrollment, as well as transient medications for other diseases or symptoms, may be allowed can be allowed at the clinical discretion of the investigators, provided that those medications are not expected to significantly affect the study results.

**Criteria for discontinuing or modifying allocated interventions**

Participants will be considered for treatment cessation and elimination from the study if they meet the following criteria: participants who are found to have not met the inclusion and exclusion criteria at the screening period due to an error, participants who experience serious adverse events (death, life-threatening, or hospitalization due to adverse events), participants with adverse events warranting discontinuation of the study intervention, participants whose symptoms worsen and require another treatment, participants who withdraw their consent, participants who are lost to follow-up, and participants who are unsuitable for continuing administration by the investigators.
Outcomes

Primary outcome

The primary outcome is the mean change from the baseline CAPS-5 score at week 6 (post-treatment). CAPS-5 is a representative clinician rating scale for PTSD. The CAPS-5 score will be measured at baseline, week 6 (post-treatment), and week 12 (follow-up). The mean change in CAPS-5 scores between baseline and week 6 will be the primary outcome.

Secondary outcomes

The mean change from the baseline CAPS-5 score at week 12 (follow-up), as well as the proportions of participants achieving criteria-based and symptom-based remissions of PTSD at week 6 (post-treatment) and week 12 (follow-up) will be secondary outcomes used to assess the severity of PTSD symptoms. Criteria-based and symptoms-based remissions of PTSD will be defined based on the results of CAPS-5. Criteria-based remission of PTSD will be defined as no longer meeting the diagnostic criteria for PTSD, which includes experiencing fewer than the required number of symptoms in each criterion. Meanwhile, a total CAPS-5 score <20 will be defined as the symptom-based remission of PTSD. Additionally, PCL-5 will be used as a self-rating scale to assess the severity of PTSD symptoms. BDI-II and BAI will be used to assess the severity of depression and anxiety symptoms, respectively. Additionally, PHQ-15 and the Insomnia Severity Index (ISI) will be used to assess the severity of somatic symptoms in patients with PTSD. To evaluate the quality of life in patients with PTSD, EQ-5D-5L and WHOQOL-BREF scores will be used as secondary outcomes.

Safety outcomes

The incidence of adverse events will be presented in three groups based on severity and causality assessment. The occurrence of adverse events will be monitored at every visit. Additionally, the suicide risk will be evaluated by the investigators using C-SSRS at screening, week 6 (post-treatment), and week 12 (follow-up).

Exploratory outcomes

Exploratory outcomes will be measured before and after the intervention (weeks 0 and 6). Structural and functional brain images will be obtained using 3T MRI. Emotional tasks that
induce emotions of joy, anxiety, and sadness by watching video clips will be conducted, and the facial expressions of participants during the tasks will be recorded. The facial expression analysis will be conducted using iMotions software. In addition, empathy quotient, and irritable bowel severity symptom severity scale will be measured as exploratory outcomes. Figure 2 summarizes the participant timeline.

Sample size

The sample size was computed to detect the mean difference in change from the baseline CAPS-5 score after treatment between the EFT and WL groups. No previous study has compared the CAPS-5 scores between EFT and WL. We estimated that EFT would have an effect size similar to that of EMDR, and in a previous study comparing EMDR with WL, the effect size (Cohen’s $d$) of EMDR was 0.65. With a two-sided significance level of 0.05 and a power of 0.8, 38.14 participants are required in each group. Considering a dropout rate of 5%, 40 participants will be recruited per group, and a total of 120 will be investigated. The dropout rate was calculated based on a previous feasibility trial of EFT in patients with PTSD.

Additionally, we calculated the required sample size to evaluate the non-inferiority of EFT compared to WET. Under the assumptions of a significance level of 0.05, power of 0.8, standard deviation of 17, mean difference of 0, and a non-inferiority margin of 10, the estimated sample size per group is 36, without accounting for dropout rates.

Recruitment

To achieve adequate participant recruitment, regular advertisements will be conducted through online media, and approved materials will be attached to the bulletin boards inside and outside of the hospital. In the case of delayed recruitment, local advertisement can be implemented. The first participant of the study was enrolled on December 8th, 2022, and the date of the last observation is expected to be completed in December 2025.

Allocation

Random assignment will be performed in compliance with group assignments that are not biased and not exposed to participants and researchers. An independent statistician who is not involved in the performance and evaluation of this clinical trial generated a random assignment sequence in
a 1:1:1 ratio for each group using blocked randomization in SAS® (version 9.4, SAS Institute Inc., Cary, NC, USA). The generated random sequence table will be kept by the independent statistician and protected from disclosure.

For each random number, the assignment results will be sealed in an opaque envelope and stored in a locked cabinet. Participants’ random numbers will be assigned according to the order in which the participants are enrolled at visit 2 after the screening process. A random number will be given independently of the screening number. The corresponding envelope will be opened according to the random number, and group assignment will be performed. The date and time of opening and the signature of the researcher who opened it will be written on the open envelope and stored separately.

**Blinding**

The participants will be allocated to the EFT, WET, or WL groups, and it is impossible to blind therapists and participants during the intervention. Nevertheless, this study is designed as an assessor-blinded trial to control for bias as much as possible. Effectiveness and suicide risk will be evaluated by independent assessors who have not performed the intervention procedure or random assignment. Visits for interventions (3–7) and assessment (2, 8, and 9) will be separated.

**Data collection methods**

To assess the severity of PTSD symptoms, the CAPS-5 (clinician-administered tool) and PCL-5 (self-reported instrument) will be used. The CAPS-5 consists of 30 items measuring the severity of PTSD symptoms, and the total score ranges from 0 to 80, with higher scores indicating more severe symptoms. The validated Korean version of the CAPS-5 will be used. CAPS-5 will be evaluated by qualified investigators. To ensure the consistency of CAPS-5, an investigator meeting was conducted for training before study initiation. The PCL-5 consists of 20 items measuring the severity of PTSD symptoms in the DSM-5, and the total PCL-5 score ranges from 0 to 80, with higher scores indicating severe symptoms. The validated Korean version of the PCL-5 will be used. To assess PTSD and depressive symptoms during the intervention period, the PCL-5 and BDI-II will be measured every 2 weeks. The BDI-II consists of 21 items, and the total score ranges from 0 to 63, with higher scores indicating more severe symptoms. A validated Korean version of the BDI-II will be used. Even if a participant withdraws consent, efforts will be made to schedule an evaluation visit for the CAPS-5.
Data management

Data in source documents (assessment sheets completed by investigators, questionnaires filled out by participants, and electronic medical records) will be entered into the electronic Case Report Form (eCRF). The eCRF was developed using the iCReaT (internet-based Clinical Research and Trial) system provided by the Korea National Institute of Health. A data management plan was prepared before study initiation. Data specifications were defined and source documents for each data point were agreed upon. Investigators at the institute were trained for data entry and coding using the eCRF system. The data entered in the eCRF will be checked bimonthly after enrolment of the first participant.

Statistical methods

Analysis sets

The analysis sets will be defined as follows. 1) Full analysis (FA) set: Population that complies with the intention-to-treat principle, meets major inclusion and exclusion criteria, and has obtained at least one primary outcome assessment after the baseline assessment. 2) Per protocol set: Population within the FA set who have ≥80% compliance with the interventions, do not take any prohibited medications, and do not have major violations to the protocol. 3) Safety analysis set: Population consisting of all participants whose safety assessment has been made at least once since the randomized allocation.

Statistical methods for analyzing the primary outcome

This is a multi-arm parallel-group randomized trial, and there are three hypotheses for the primary outcome. The first null hypothesis is that the mean change from baseline at week 6 in the EFT group will be the same as that in the WL group \( H_0: \mu_1 = \mu_2, H_1: \mu_1 \neq \mu_2 \). A mixed-effect model repeated measure (MMRM) will be used, with group and time as fixed factors, and participant as a random factor. The mean difference and 95% CI between two groups and p-values will be presented. The first hypothesis aims to assess the effect size of EFT on PTSD symptoms compared with WL. The second null hypothesis is that the mean change from baseline at week 6 in the WET group will be the same as that in the WL group \( H_0: \mu_3 = \mu_2, H_1: \mu_3 \neq \mu_2 \). MMRM will be used as in the first hypothesis. From the results of the second hypothesis, the non-inferiority margin (M) will be defined. The lower limit of the 95% CI of the mean difference between two groups will be M.
The third null hypothesis is that the mean change from the baseline at week 6 in the WET and EFT group will be greater than M ($H_0 : \mu_3 - \mu_1 > M$, $H_1 : \mu_3 - \mu_1 \leq M$). The third hypothesis assesses the non-inferiority of EFT compared with WET, and M calculated in the second hypothesis will be used. MMRM will be used, similar to the first hypothesis, but the significance level will be set to 2.5% since the non-inferiority test is one-sided.

The problem of multiple testing will be solved using the fixed sequence method. If the statistical result for hypothesis 1 is significant, the tests for hypotheses 2 and 3 will be performed. If the first null hypothesis were not rejected, tests for hypotheses 2 and 3 will not be performed. If the first null hypothesis is rejected and the test for hypothesis 2 is performed, in case that the statistical result for hypothesis 2 is significant, the test for hypothesis 3 will be conducted.

Statistical methods for analyzing the secondary outcomes

Continuous variables (mean changes in CAPS-5, PCL-5, BDI-II, BAI, PHQ-15, ISI, EQ-5D-5L, WHOQOL-BREF, and Clinical Global Impression scores) will be tested using the same method as for the primary outcome. Additionally, to compare the difference between before and after the intervention in each group, the Student paired t-test or Wilcoxon signed-rank test will be used. Repeated measures analysis of variance will be performed to test the interaction between group and time.

Binary variables (criteria-based remission of PTSD and symptom-based remission of PTSD) will be tested using logistic regression analysis. Odds ratios (95% CI) for the two groups will be presented.

Hypothesis setting and multiple-testing problem-solving methods will be the same as those used for the primary outcome.

Statistical methods used to handle missing data

The primary outcome will be analyzed using MMRM. The MMRM considers missing data using the maximum likelihood, and does not require the process of replacing the missing data. In the case of an additional analysis of covariance, missing data will be replaced using the multiple imputation method.
Data monitoring

Considering the low risk of interventions and the study purpose, a data monitoring committee is not needed. An interim analysis is not planned. If intervention-related moderate or severe adverse events occur in >25% of all participants, the study will be stopped.

Harms

Adverse events will be carefully recorded at every visit, and the frequency, severity, and causality of the adverse events will be assessed in the three groups. Additionally, the suicide risk of the participants will be evaluated using the Columbia Suicide Severity Rating Scale.

Auditing

Monitoring will be conducted to verify that the clinical study data are accurate and complete, and that the clinical study is performed in accordance with the approved protocol and related regulations. Monitoring of clinical studies will be conducted through regular visits to the institute. The scope of monitoring will include compliance with the clinical study protocol, collection of appropriate and accurate data, obtaining informed consent, and recording adverse events. The monitor will check the eCRF, source documents, and essential documents during regular visits.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

Research ethics approval

This study has been approved by the Institutional Review Board (IRB) of the Kyung Hee University Korean Medicine Hospital (KOMCIRB2021-11-005-001).
Protocol amendments

Protocol modifications will be determined after sufficient discussion by investigators at the hospital and KIOM and will be applied to the study after obtaining approval for the amendment from the IRB. The current version of protocol is 1.7 (date: 2023-03-28).

Consent or assent

Written informed consent will be obtained from all participants prior to screening (online supplemental material S1). The principal investigator and sub-investigators, who are Korean medicine doctors in the hospital and delegated by the principal investigator, will provide information about the clinical study and obtain informed consent from the participants. Informed consent and a description of the study approved by the IRB will be used. Sufficient time and opportunity for the participants to ask questions about the details of the clinical study and to decide whether to participate will be provided. Additional consent will be obtained for the collection and analysis of blood samples.

Confidentiality

The personal information of each participant will not be entered into eCRF, and the data of each participant will be collected under screening and random numbers.

Ancillary and post-trial care

Follow-up observation and online follow-up observation will be conducted at weeks 12 and 24. Compensation criteria and plans will be prepared for those who suffer harm from trial participation. The occurrence of adverse events will be assessed at every visit, and the required treatment and observation will be applied until the symptoms disappear.

Dissemination policy

The clinical study information and results will be registered with the Clinical Research Information Service. This study’s findings will be presented at conferences and published in peer-reviewed journals. The participant-level dataset will be uploaded to the Korean Medicine Data Repository (kmdr.kiom.re.kr) after study completion.
Author contributions

H Kim, SH Cho, Y Choi, Y Kim, and S Choi conceived the trial. YE Choi, O Kwon, D Kwon, and S Lee helped with study implementation. Y Choi and Y Kim completed the initial draft of the manuscript. O Kwon generated the randomization sequence and provided biostatistical advice and information. All authors designed the study and read, edited, and approved the final manuscript and supplementary files.

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Competing interests

None declared.

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Figure legends

Figure 1 Flow diagram.

LEC-5, Life Event Checklist for DSM-5; CTQ, Childhood Trauma Questionnaire; SCID-5, Structured Clinical Interview for DSM-5; C-SSRS, Columbia Suicide Severity Rating Scale; CAPS-5, Clinician-Administered PTSD Scale; CGI-S, Clinical Global Impressions-Severity scale; CGI-I, Clinical Global Impressions-Improvement scale; PCL-5, PTSD Checklist-5; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Index; PHQ-15, Patient Health Questionnaire-15; ISI, Insomnia Severity Index; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; WHOQOL-BREF, WHO QoL assessment instrument abbreviated version; EQ, empathy Quotient; IBS-SSS, Irritable Bowel Symptoms Severity Scale.

Figure 2 The schedule of enrolment, intervention and assessment.

1 The participants assigned to WL will not receive any intervention until completion of the follow-up visit. After 12 weeks, EFT will be applied to participants in the WL group.

2 The facial expressions will be recorded during the emotional task.

EFT, Emotional Freedom Techniques; WET, Written Exposure Therapy; WL, Waiting List; CAPS-5, Clinician-Administered PTSD Scale; CGI-S, Clinical Global Impressions-Severity scale; CGI-I, Clinical Global Impressions-Improvement scale; PCL-5, PTSD Checklist-5; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Index; PHQ-15, Patient Health Questionnaire-15; ISI, Insomnia Severity Index; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; WHOQOL-BREF, WHO QoL assessment instrument abbreviated version; EQ, empathy Quotient; IBS-SSS, Irritable Bowel Symptoms Severity Scale.
Visit 1
Screening
~2weeks

Screening: Informed consent, Demographics, Medical history, Physical examination, Blood test, LEC-5, CTQ, SCID-5, C-SSRS, Eligibility assessment

Visit 2
Baseline
Week 0

Total N: 120

Randomization

Visit 3~7
Intervention
Week 1~5

EFT
N=40

WET
N=40

WL
N=40

EFT or WET (Visit 3~7), PCL-5, BDI-II (Visit 4, 6)

Visit 8
Post-treatment
Week 6


Visit 9
Follow-up
Week 12


Visit 10
Close-out
Week 24

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<th>Visit number</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Intervention</th>
<th>Assessment</th>
<th>Follow-up</th>
<th>Close-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ -14 days</td>
<td>Visit 1</td>
<td>X</td>
<td>X</td>
<td>Visit 3 ~ Visit 7</td>
<td>Visit 8</td>
<td>Visit 9</td>
<td>Visit 10</td>
</tr>
<tr>
<td>Week 0</td>
<td>Visit 2</td>
<td>X</td>
<td>X</td>
<td>Week 6</td>
<td>Week 12</td>
<td>Week 24</td>
<td></td>
</tr>
<tr>
<td>Week 1~ Week 5</td>
<td>Visit 3 ~ Visit 7</td>
<td>X</td>
<td>X</td>
<td>Week 12</td>
<td>Week 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**ENROLMENT:**
- Informed consent X
- Eligibility screen X
- C-SSRS X X X
- Allocation X

**INTERVENTIONS:**
- EFT X X X X X
- WET X X X X X
- WL

**ASSESSMENTS:**
- CAPS-5 X X X
- CGI-S X X
- CGI-I X X
- PCL-5, BDI-II X X X X X X
- BAI X X X
- PHQ-15, ISI X X
- EQ-5D-5L, WHOQOL-BREF X X X
- MRI X X
- Emotional task X
- EQ, IBS-SSS X X
S1. Informed Consent Form (Translated English version)

Informed Consent Form

<table>
<thead>
<tr>
<th>Study title</th>
<th>Emotional Freedom Techniques vs Written Exposure Therapy vs Waiting List for Posttraumatic Stress Disorder: A Randomized Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Department of Neuropsychiatry, KyungHee University Korean Medicine Hospital, KyungHee University Medical Center 23, Kyungheedae-ro, Dongdaemun-gu, Seoul Prof. Seung-Hun Cho</td>
</tr>
<tr>
<td>Sub-Investigator</td>
<td>Department of Neuropsychiatry, KyungHee University Korean Medicine Hospital, KyungHee University Medical Center 23, Kyungheedae-ro, Dongdaemun-gu, Seoul</td>
</tr>
<tr>
<td>Study Site</td>
<td>Department of Neuropsychiatry, KyungHee University Korean Medicine Hospital, KyungHee University Medical Center 23, Kyungheedae-ro, Dongdaemun-gu, Seoul</td>
</tr>
<tr>
<td>Source of Monetary/Material Support</td>
<td>Korea Institute of Oriental Medicine</td>
</tr>
<tr>
<td>Institutional Review Board</td>
<td>Kyung Hee University Korean Medicine Hospital Institutional Review Board 23, Kyungheedae-ro, Dongdaemun-gu, Seoul</td>
</tr>
</tbody>
</table>

This information sheet and consent form have been prepared to provide you with an explanation of the content of the clinical study and your role, compensation, and other relevant details. It is important that you fully understand why this clinical study is being conducted and what your involvement will entail before making a voluntary decision to participate. Take sufficient time to read this information sheet, and if desired, consult with your family or other individuals. You have the right to withdraw from the study at any time if you wish. If you have any questions, feel free to ask the principal investigator or research coordinator and take the necessary time to decide whether or not to participate in this clinical study. The research team will be available to answer your questions before, during, and after the study. Once you have thoroughly reviewed and agreed to the contents of this information sheet, please sign the consent form. You will receive one copy each of this information sheet and the signed consent form.

1. Background and Objectives of the Study

This clinical study is conducted for research purposes to evaluate the effectiveness and safety of Emotional Freedom Techniques for Posttraumatic Stress Disorder (PTSD). PTSD is a condition that manifests with characteristic symptoms following exposure to traumatic events such as death, severe injury, or sexual assault. These symptoms include intrusive recollections of the traumatic event, distressing dreams, persistent avoidance of stimuli associated with the trauma, negative changes in cognition and mood related to the event, and heightened arousal and reactivity.
associated with the trauma.

2. Study Participants
A total of 120 participants, aged 19 years or older but under 65 years, with symptoms of PTSD, and 60 participants, aged 19 years or older but under 65 years, without a history of trauma, will be enrolled in this clinical study.

3. Information about the Intervention (Applicable to the patient group only)
Emotional Freedom Techniques (EFT) is a combination of traditional East Asian medicine’s meridian theory and psychotherapeutic techniques, forming a meridian-based psychotherapy. Previous research has reported the effectiveness of EFT in improving symptoms of PTSD. Clinical studies applying EFT to patients with anxiety disorders and insomnia have been conducted in Korea.

In this clinical study, participants will be divided into three groups: the EFT group, the Written Exposure Therapy (WET) group, and the Waiting List group. If assigned to the EFT group, you will receive EFT sessions once a week for a total of five weeks. If assigned to the WET group, you will receive WET sessions once a week for a total of five weeks. WET is one of the most extensively researched psychotherapeutic methods known to be effective in improving symptoms of PTSD. If assigned to the Waiting List group, after the 12-week assessment period, you will receive EFT sessions once a week for a total of five weeks.

4. Method of Group Assignment (Applicable to the patient group only)
Once you have been determined as eligible for this clinical study through screening evaluations and tests, you will be randomly assigned to one of the three groups in a 1:1:1 ratio according to a predetermined randomization table. The group assignment is purely random and does not involve any intentional decision based on individual characteristics or issues. It follows a random allocation method (similar to flipping a coin), and the probability of being assigned to each group is equal.

5. Procedures You Will Receive During Study Participation
   - For the PTSD patient group:

If you agree to participate in this clinical study and sign the written consent form, you will undergo a medical history interview, vital sign measurements, questionnaires, laboratory tests, and other relevant assessments to determine your eligibility for this clinical study. If you do not meet the inclusion and exclusion criteria based on the screening results, you will not be able to participate in the study. During the screening visit, specific tests and evaluations will be conducted to assess your eligibility according to the predetermined inclusion/exclusion criteria. If you meet the criteria, you will be randomly assigned to one of the three groups in a 1:1:1 ratio according to the predetermined randomization table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Emotional Freedom Techniques Group</th>
<th>Written Exposure Therapy Group</th>
<th>Waiting List Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>
Once you participate in the clinical study, you will need to visit again within 14 days for an initial assessment (week 0), including an MRI examination. If you are assigned to the Emotional Freedom Techniques or Writing Exposure Therapy group, you will receive treatment once a week for a total of 5 sessions. After the completion of treatment (6 weeks), you will undergo a post-treatment evaluation, including an MRI examination. At 12 weeks from the initial assessment, you will visit again for follow-up observation. At 24 weeks from the initial assessment, you will be required to complete an additional online survey. If you are assigned to the Waiting List group, you will not start the Emotional Freedom Technique treatment immediately. Instead, after the completion of the 12-week follow-up observation, you will receive Emotional Freedom Techniques treatment once a week for a total of 5 sessions.

The specific visit schedule and contents for the clinical study are as follows:

**<Clinical Study Schedule - PTSD Patient Group, Assigned to EFT or WET Group>**

<table>
<thead>
<tr>
<th>Time point</th>
<th>Week 0</th>
<th>Week 1~ Week 5</th>
<th>Week 6</th>
<th>Week 12</th>
<th>차</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Number</td>
<td>V1</td>
<td>V2</td>
<td>V3~V7</td>
<td>V8</td>
<td>V9</td>
</tr>
<tr>
<td>Written consent</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history taking</td>
<td></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>Height/weight</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric interview and</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>assessment</td>
<td>O</td>
<td></td>
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<td></td>
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<tr>
<td>Suicide risk assessment</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Schedule</td>
<td>Week 0</td>
<td>Week 6</td>
<td>Week 12</td>
<td>Week 13 - Week 17</td>
<td>Week 24</td>
</tr>
<tr>
<td>----------------</td>
<td>--------</td>
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</tr>
<tr>
<td><strong>Borderline personality assessment</strong></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inclusion/exclusion criteria</strong></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Random allocation</strong></td>
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<td></td>
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<tr>
<td><strong>PTSD symptoms evaluation</strong></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td><strong>MRI scan</strong></td>
<td>O</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Emotional tasks</strong></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood sample collection</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other questionnaires</strong></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EFT or WET</strong></td>
<td>O</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Monitoring of concomitant medications</strong></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td><strong>Monitoring of adverse events</strong></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td><strong>Visit schedule</strong></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td><strong>Completion of the study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>O</td>
</tr>
</tbody>
</table>

<Clinical Study Schedule - PTSD Patient Group, Assigned to WL Group>
For the healthy control group:

If you agree to participate in this clinical study and sign the written consent form, you will undergo a medical history interview, vital signs measurement, questionnaire, and laboratory tests to determine your eligibility for the study. If the screening test results do not meet the inclusion and exclusion criteria, you will not be able to participate in the research. During the screening visit, you will undergo the designated tests and evaluations to determine if you meet the inclusion/exclusion criteria for this clinical study. If you meet the criteria, you will be enrolled in the study and the next visit schedule will be determined. Within 14 days, you will return for an evaluation, including an MRI scan.

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>60</td>
</tr>
</tbody>
</table>

Here is the specific visit schedule and content:

<Clinical Study Schedule – Healthy control Group>

<table>
<thead>
<tr>
<th>Time point</th>
<th>Week 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Number</td>
<td>V1</td>
</tr>
<tr>
<td>Written consent</td>
<td>O</td>
</tr>
<tr>
<td>Demographics</td>
<td>O</td>
</tr>
<tr>
<td>Medical history taking</td>
<td>O</td>
</tr>
<tr>
<td>Physical examination</td>
<td>O</td>
</tr>
<tr>
<td>Vital signs</td>
<td>O</td>
</tr>
<tr>
<td>Height/weight</td>
<td>O</td>
</tr>
<tr>
<td>Depression, Anxiety, Somatic</td>
<td>O</td>
</tr>
<tr>
<td>symptoms questionnaire</td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>O</td>
</tr>
</tbody>
</table>
6. Expected Duration of Participant
   - For the PTSD patient group:

   The expected duration of your participation in this clinical study is approximately 24 weeks. During the initial visit for screening, the examination will take about 1-2 hours. If you are enrolled, you will need to visit within 2 weeks for the initial evaluation, which includes an MRI scan, and it will take approximately 3 hours. When receiving the Emotional Freedom Techniques (EFT) or Written Exposure Therapy (WET), you will have weekly visits with each session lasting approximately 1 hour and 30 minutes. At the 6-week visit, another evaluation including an MRI scan will be conducted, taking approximately 3 hours. At the 12-week visit, an assessment of major symptoms related to post-traumatic stress disorder (PTSD) will be performed, and it is expected to take about 1 hour.

7. Potential Discomfort or Risks Associated with Study Participation

   In this clinical study, blood collection is required for examinations and blood sample analysis. Throughout the study period, there will be a total of three blood collection procedures (two for the healthy control group), with approximately 10ml of blood collected per procedure, which is a typical amount for blood tests. While the risks associated with blood collection are generally low, it is possible to experience pain during the procedure. Needle puncture may cause local pain, bruising, dizziness, and rarely, fainting or an infection at the puncture site. If you experience any discomfort after the blood collection, please inform the investigators.

8. Expected Benefits of Participation

   By participating in this study and receiving either Emotional Freedom Techniques (EFT) or Written Exposure Therapy (WET), it is anticipated that there will be improvements in PTSD symptoms. However, it cannot be guaranteed that
your condition will necessarily improve as a result of participating in this study. By participating in this clinical research, it is expected that you and other patients involved may benefit from the findings of this study in the future. Additionally, your participation may contribute to the development of new treatment approaches for other patients. It is important to note that participating in this clinical study is not the only option for the treatment of your PTSD symptoms.

9. Alternative Treatment Options
When it comes to treating PTSD, the first consideration is psychotherapy focused on trauma and the use of antidepressant medication. Psychotherapeutic approaches for PTSD include cognitive-behavioral therapy (CBT), cognitive processing therapy, exposure therapy, prolonged exposure therapy, eye movement desensitization and reprocessing (EMDR), narrative exposure therapy, stress inoculation training, and stage-based treatment. Traditional Korean medicine approaches such as Gyeongja Pyeongji therapy, Jieon Goron therapy, Ijeongbyeon-gi therapy, and Ojisangseung therapy can also be applied.

10. Participant Responsibilities
The following guidelines are essential for ensuring participant protection and accurate research conduct:
① Adhere strictly to the scheduled visits and examinations.
② Inform the investigator in detail before starting any new medication during the study period, including both current medications and any additional ones.
③ Refrain from seeking symptom-improvement therapies during the study period to exclude the effects of other treatments.
④ Participants who are pregnant or breastfeeding cannot participate in the study for safety reasons. If you are capable of becoming pregnant, please inform us of the contraceptive method you are using, and if your contraceptive method is not reliable, you cannot participate in the study.

11. Expected Participant Costs
By participating in this study, there are no additional costs incurred for the participants. You will not be responsible for any medical or examination fees associated with the clinical study during your participation. However, any unrelated hospitalization expenses or consultation fees incurred during or after the study period will be your responsibility.

Additionally, participants who take part in the clinical study will receive a reimbursement of 50,000 won per visit for transportation expenses and questionnaire completion costs. The reimbursement for transportation expenses will be processed within approximately 20 to 30 days after each visit, considering the necessary administrative procedures. Please take this into account when participating in the study.

13. Compensation and Treatment Measures in Case of Harm
The research team will take the necessary measures according to the clinical study protocol and handle any medical issues directly related to the research. In the event of direct injury or health damage resulting from participation in this clinical research, you will be eligible for compensation through the "Compensation Agreement" and the Clinical
Research Injury Insurance. However, damages not directly caused by participation in the clinical study may be excluded from compensation.

The principles of compensation are as follows:

① Compensation will be provided for physical injuries suffered by participants due to unexpected incidents or side effects during the course of the clinical study.
② Compensation will be provided if the injury is caused by an intervention related to the clinical study.
③ Compensation will be provided for injuries resulting in sustained disabilities, rather than temporary pain or easily treatable injuries.
④ Compensation will be provided for injuries directly caused by the intervention of the clinical study or during the process of managing side effects.

In the event of any injury or adverse event related to the clinical study, you must immediately inform the investigator.

14. Participant’s Decision and Withdrawal from the Clinical Study

The decision to participate in this clinical study is entirely voluntary and up to your free will. You have the right to decide not to participate in the study at any time, and you also have the option to withdraw from the study. If you wish to discontinue your participation, please inform the investigator.

In the event that you withdraw from the study after the initial evaluation, any scheduled tests (vital signs, laboratory tests, etc.) and assessments (questionnaires) within 7 days of the withdrawal will be conducted at the discretion of the investigator.

You will not experience any disadvantages by choosing not to participate in this research, and your decision to refuse or discontinue participation in the clinical study can be made without any loss of benefits that you would normally receive. By signing the form or giving consent to participate in the study, please be aware that you are not waiving your legal rights to protection. If you decide to withdraw from or revoke your consent for the clinical study, your information will no longer be collected thereafter. However, the information collected up to that point may be accessed by relevant investigators within the bounds of confidentiality regarding your personal data protection.

15. Suspension of Participant’s Involvement in the Research and Reasons

Your participation in this study may be suspended under the following circumstances:

① If a participant is found to have not met the inclusion and exclusion criteria at the screening period due to an error.
② If a systemic disorder that was not detected during the screening examination is discovered.
③ If a participant experiences a serious adverse event (death, life-threatening, or hospitalization due to adverse events)
④ If an adverse event is deemed serious enough by the investigator to be inappropriate for continued participation.
⑤ If symptoms worsen, and the investigator determines that another treatment is necessary.
⑥ If a participant withdraws their consent for clinical study participation or requests to discontinue their involvement.
⑦ If a participant’s visits and follow-ups cannot be conducted.
8. If, in the researcher’s judgment, continuing administration of the clinical study is deemed unsuitable for other reasons.

If a participant’s involvement in the clinical study is suspended during the study, they will be informed of these circumstances. In the event that the participation is discontinued due to an adverse reaction, necessary tests to assess your health status and receive optimal treatment will be provided to ensure appropriate management. In the case of a serious adverse event, the study will be suspended, and prompt and appropriate measures will be taken.

16. Access to Records and Protection of Personal Information

To ensure the validity of this clinical study and verify the procedural integrity and reliability of the data without compromising the confidentiality of participants, monitors, auditors, and the Institutional Review Board (IRB) of the study site may directly access your medical records within the limits set by relevant regulations. Your signature on the consent form indicates your permission to allow direct access to these records by authorized individuals. All personal information, including your identity and clinical trial data, will be strictly kept confidential and protected. While study results may be shared with relevant researchers for the purpose of the study, your personal information will be safeguarded, with only initials or pseudonyms being disclosed to protect your privacy. In the event of publication of the clinical study findings, your personal information will remain confidential.

The personal information collected from your participation in this study includes your name, contact information, demographic characteristics, personal medical history, and bank account number. This information will be stored and used for research purposes for a period of 3 years after the study’s completion. The collected information will be strictly managed in accordance with the "Personal Information Protection Act" and other applicable regulations. Personal information will be stored in secure locations with access controls (such as data management rooms), and electronic documents will be encrypted. Only the principal investigator and authorized investigators will have access to this information. We will make every effort to ensure the confidentiality of all personal information obtained through the study. When personal information obtained from the study is published in journals or conferences, your name and other personal identifiers will not be used.

Personal information-related materials will be stored, managed, and provided for disposal for a maximum of 3 years from the completion of the study, or upon request for information disposal. Personal information that has exceeded the retention period will be destroyed in accordance with Article 16 of the "Personal Information Protection Act" Enforcement Decree. However, research data may be used beyond 3 years for public purposes, related research, or medical purposes, provided that they are anonymized.

Furthermore, collected personal information and sensitive information may be provided to third parties such as the Korea Institute of Oriental Medicine (KIOM) and data processing agencies for the purpose of organizing clinical study data, scientific research, and preservation of public interest records, as stipulated in Article 18 of the Bioethics Act. In such cases, your research information will be anonymized and shared with third parties after deliberation by the Institutional Review Board. Your signature on this consent form will be considered as prior knowledge and acceptance of these provisions.

17. Research Data Sharing Plan
After the completion of the clinical study, anonymized and organized data, including brain imaging data, of the participants may be registered in the Korean Medicine Data Repository (kmdr.kiom.re.kr), which is a publicly accessible or partially accessible database for managing and sharing research data in Korean medicine R&D. This system serves as a platform for registering research data conducted with public resources. Additionally, the anonymized data and brain imaging data may be used for public purposes, such as uploading to public data servers required for submitting scientific papers or for neuroscience-related research.

18. Inquiries Regarding the Study

If you have any questions, concerns, or discomfort related to this study, or if any harm occurs as a result of the clinical study, please consult with our research team. If you need to contact us regarding the study, you or your legal guardian can schedule a telephone consultation at any time. The contact information for the available research team members is provided below. If you wish to discuss questions, concerns, complaints, or the rights of the participants, you may also consult with the Institutional Review Board (IRB) of our institution.

If you have chosen to participate in this study, you will receive a copy of the signed informed consent form.

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation and Position</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>KyungHee University Korean Medicine Hospital /Principal investigator</td>
<td>☎</td>
<td></td>
</tr>
<tr>
<td>KyungHee University Korean Medicine Hospital /Sub-investigator</td>
<td>☎</td>
<td></td>
</tr>
<tr>
<td>KyungHee University Korean Medicine Hospital /Clinical Research Coordinator</td>
<td>☎</td>
<td></td>
</tr>
<tr>
<td>Kyung Hee University Korean Medicine Hospital Institutional Review Board</td>
<td>☎</td>
<td></td>
</tr>
</tbody>
</table>
Consent to Participate

<table>
<thead>
<tr>
<th>Study title</th>
<th>Emotional Freedom Techniques vs Written Exposure Therapy vs Waiting List for Posttraumatic Stress Disorder: A Randomized Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Department of Neuropsychiatry, KyungHee University Korean Medicine Hospital, KyungHee University Medical Center 23, Kyungheedae-ro, Dongdaemun-gu, Seoul Prof. Seung-Hun Cho</td>
</tr>
<tr>
<td>Sub-Investigator</td>
<td>Department of Neuropsychiatry, KyungHee University Korean Medicine Hospital, KyungHee University Medical Center 23, Kyungheedae-ro, Dongdaemun-gu, Seoul</td>
</tr>
<tr>
<td>Study Site</td>
<td>Department of Neuropsychiatry, KyungHee University Korean Medicine Hospital, KyungHee University Medical Center 23, Kyungheedae-ro, Dongdaemun-gu, Seoul</td>
</tr>
<tr>
<td>Source of Monetary/Material Support</td>
<td>Korea Institute of Oriental Medicine</td>
</tr>
<tr>
<td>Institutional Review Board</td>
<td>Kyung Hee University Korean Medicine Hospital Institutional Review Board 23, Kyungheedae-ro, Dongdaemun-gu, Seoul</td>
</tr>
</tbody>
</table>

*** Please carefully read the following information and have a thorough discussion with the investigator. If you voluntarily agree, please check the box. ***

1. I have read the explanation of this study and have discussed it with the responsible researcher. □
2. I have been informed about the risks and benefits of this study and have received satisfactory answers to my questions. □
3. I have received sufficient explanations from the researcher regarding the benefits and risks associated with this study, and I understand that I can request further explanations from the researcher at any time regarding these matters. □
4. I voluntarily agree to participate in this study. □
5. I understand that I can withdraw from this study at any time and that this decision will not have any negative consequences for me. □
6. I consent to the collection and processing of information about me obtained in this study by the investigators, within the limits allowed by current laws and institutional review board regulations. □

7. I agree that after the completion of the study, collected data that has been processed in an anonymized format may be registered in a publicly accessible database. □

**<Collection and Use of Personal Information>**

<table>
<thead>
<tr>
<th>Personal information items</th>
<th>Purpose of collection</th>
<th>Retention period</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Name, Sex, Birth Date</td>
<td>Evaluation of the effectiveness and safety of Emotional Freedom Technique for patients with PTSD</td>
<td>3 years after the completion of the study</td>
</tr>
<tr>
<td>B. Education, Employment Status, Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Resident Registration Number, Phone Number, Address, Bank Account Number</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

※ You have the right to refuse to provide personal information.
☞ Do you agree to the collection and use of personal information as stated above? (□ Yes, □ No)

**<Collection and Use of Sensitive Information>**

<table>
<thead>
<tr>
<th>Sensitive information items</th>
<th>Purpose of collection</th>
<th>Retention period</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Health (current and past medical history, medication history, etc.)</td>
<td>Evaluation of the effectiveness and safety of Emotional Freedom Technique for patients with PTSD</td>
<td>3 years after the completion of the study</td>
</tr>
<tr>
<td>B. Facial images obtained from the Emotional tasks (the images are stored in numerical format, and recorded video data is permanently deleted from the storage device within 1 year of acquisition)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

※ You have the right to refuse to provide sensitive information.
☞ Do you agree to the processing of sensitive information as stated above? (□ Yes, □ No)

**<Disclosure and Outsourcing of Personal Information to Third Parties>**

<table>
<thead>
<tr>
<th>Recipient of Disclosure</th>
<th>Personal Information Disclosed</th>
<th>Purpose of collection</th>
<th>Retention period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korea Institute of Oriental Medicine</td>
<td>A. Sex, Date of Birth</td>
<td>Evaluation of the effectiveness and safety of Emotional Freedom Technique</td>
<td>3 years after the completion of the study</td>
</tr>
<tr>
<td></td>
<td>B. Education, Employment Status, Marital Status</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
C. Health (current and past medical history, medication history, smoking history, alcohol consumption history, etc.)

D. Facial images obtained from the Emotional tasks (the images are stored in numerical format, and recorded video data is permanently deleted from the storage device within 1 year of acquisition)

※ You have the right to refuse third-party disclosure and outsourcing. Do you agree to the processing of personal information as described above? (☐ Yes, ☐ No)

8. I agree that the research team and authorized representatives, including monitoring agents, inspection agents, institutional review boards, the Minister of Health and Welfare, and the Director of the Food and Drug Administration, may have access to my medical records within the scope of protecting the confidentiality of my personal information, in order to verify the implementation procedures and data quality of the research in accordance with relevant laws and regulations. I also understand that the signed consent form allows for the access to such information. ☐

9. I agree that after the completion of the study, collected data that has been processed in an anonymized format may be registered in a publicly accessible database. ☐

10. My signature indicates that I have received a copy of this informed consent form and will keep a copy until the end of my participation in the study. ☐

I have fully understood the contents of the consent form and hereby agree to the above statements by signing below.

If employees of the study site participate:

I voluntarily participated in this study (handwritten)
<table>
<thead>
<tr>
<th>Role</th>
<th>Name:</th>
<th>Signature:</th>
<th>Date:       /        /</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legal Guardian</td>
<td>Name:</td>
<td>Signature:</td>
<td>Date:       /        /</td>
</tr>
<tr>
<td>(if necessary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Relationship with the participant: (Parent • Spouse • Legal guardian)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Reason:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer</td>
<td>Name:</td>
<td>Signature:</td>
<td>Date:       /        /</td>
</tr>
<tr>
<td>(If necessary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor</td>
<td>Name:</td>
<td>Signature:</td>
<td>Date:       /        /</td>
</tr>
<tr>
<td>(Investigator)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
<th>Line No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
<td>1-3</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
<td>48-49</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
<td>49 (URL)</td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
<td>430</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
<td>463-467</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>4-12, 456-461</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
<td>465-467</td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background and rationale</td>
<td>6a</td>
<td>Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention</td>
<td>67-107</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Explanation for choice of comparators</td>
<td>111-113</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
<td>126-147</td>
</tr>
</tbody>
</table>
Trial design 8  Description of trial design including type of trial (eg, parallel
group, crossover, factorial, single group), allocation ratio, and
framework (eg, superiority, equivalence, noninferiority,
exploratory) 149-152

Methods: Participants, interventions, and outcomes

Study setting 9  Description of study settings (eg, community clinic, academic
hospital) and list of countries where data will be collected.
Reference to where list of study sites can be obtained 155-156

Eligibility criteria 10  Inclusion and exclusion criteria for participants. If applicable,
eligibility criteria for study centres and individuals who will
perform the interventions (eg, surgeons, psychotherapists) 158-192

Interventions 11a  Interventions for each group with sufficient detail to allow
replication, including how and when they will be administered 194-239

11b  Criteria for discontinuing or modifying allocated interventions
for a given trial participant (eg, drug dose change in response
to harms, participant request, or improving/worsening disease) 241-248

11c  Strategies to improve adherence to intervention protocols, and
any procedures for monitoring adherence (eg, drug tablet
return, laboratory tests) 226-227

11d  Relevant concomitant care and interventions that are
permitted or prohibited during the trial 232-239

Outcomes 12  Primary, secondary, and other outcomes, including the
specific measurement variable (eg, systolic blood pressure),
analysis metric (eg, change from baseline, final value, time to
event), method of aggregation (eg, median, proportion), and
time point for each outcome. Explanation of the clinical
relevance of chosen efficacy and harm outcomes is strongly
recommended 250-284

Participant
timeline 13  Time schedule of enrolment, interventions (including any run-
ins and washouts), assessments, and visits for participants. A
schematic diagram is highly recommended (see Figure) Figure 2

Sample size 14  Estimated number of participants needed to achieve study
objectives and how it was determined, including clinical and
statistical assumptions supporting any sample size
calculations 286-294

Recruitment 15  Strategies for achieving adequate participant enrolment to
reach target sample size 296-301

Methods: Assignment of interventions (for controlled trials)

Allocation:
Sequence generation 16a  Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions 304-309

Allocation concealment mechanism 16b  Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned 310-316

Implementation 16c  Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions 304-316

Blinding (masking) 17a  Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how 318-323

17b  If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial  Not applicable

Methods: Data collection, management, and analysis

Data collection methods 18a  Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol 325-337

18b  Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols 337-338

Data management 19  Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol 340-348

Statistical methods 20a  Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol 360-392

20b  Methods for any additional analyses (eg, subgroup and adjusted analyses) 396-398
20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) 351-358, 394-398

Methods: Monitoring

Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed 400-402

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial 402-403

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct 282-286, 406-408

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor 424-430

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval 437-439

Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) 441-444

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) 446-453

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable 452-453

Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial 455-457

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site 483-484

Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators 466-469
Ancillary and post-trial care  30  Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  459-463

Dissemination policy  31a  Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions  465-469

31b  Authorship eligibility guidelines and any intended use of professional writers  

31c  Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code  468-469

Appendices

Informed consent materials  32  Model consent form and other related documentation given to participants and authorised surrogates  Supplementary material

Biological specimens  33  Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  452-453

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyright by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.