ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Emotional freedom techniques versus written exposure therapy versus waiting list for post-traumatic stress disorder: protocol for a randomized clinical MRI study</th>
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<tr>
<td>AUTHORS</td>
<td>Choi, Yujin; Kim, Yunna; Choi, Sunyoung; Choi, Young Eun; Kwon, O-Jin; Kwon, Dohyeung; Lee, Seung-Ho; Cho, Seung-Hun; Kim, Hyungjun</td>
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VERSION 1 – REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Church, Dawson</th>
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<td>National Institute for Integrative Healthcare</td>
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<td>REVIEW RETURNED</td>
<td>04-Feb-2023</td>
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GENERAL COMMENTS

This is an extremely well-designed trial and most of the comments below are of a prosaic nature. This reviewer recommends publication with minor revisions.

Abstract.

In the Introduction, the authors refer to EFT as a "meridian-based psychotherapy" While this is correct, it is preferable to use "acupressure-based" since many readers will not understand what acupuncture meridians are till they are explained in the Introduction.

Also in the Introduction, they refer to "The emotional freedom technique." Emotional Freedom Techniques is always plural, because there are 48 of them, viewable at ClinicalEFT.com.

In the Introduction the authors also state that "the clinical evidence and underlying mechanisms are unknown."

However a decade of research has identified mechanisms such as attenuation of the fear response in the brain (in many MRI and EEG studies), epigenetic changes, hormonal shifts, and regulation of biomarkers like heart rate and immunoglobulins. So the mechanisms are hardly unknown.

Similarly, with over 200 clinical trials, and many meta-analyses, the clinical evidence is not unknown.

Methods. The three arm design, with WET and Wait List, is a robust design. The comparator conditions are appropriate. The large N is to be commended, with qualifications as noted below.

A further strength of the design is obtaining a categorial diagnosis of PTSD using the CAPS scale in addition to self-report.
Strengths and Limitations Section.

This section makes its points effectively. The last one, that participants cannot be blinded, could be reconsidered. Participants can be effectively blinded if they are not informed that there is a second treatment group.

It is also possible to blind clinicians by concealing the existence of a second treatment from them, though this is challenging if they work in the same institution.

Introduction

Repeat of above comments on "The emotional freedom technique" and "meridian-based psychotherapy"

The literature review should include the meta-analysis of EFT for PTSD (Sebastian & Nelms 2016) and the systematic review of EFT that included more recent PTSD research (Church, Stapleton, Vasudevan & O'Keefe, 2022).

Objectives

The assessments are appropriate. A one-item insomnia assessment, the ISI, is mentioned later, and should be added to this section. Adding a one-item pain assessment such as the Pain Rating Scale would be useful.

The eligibility criteria are appropriate, in particular the inclusion of patients with mild TBI, since the symptoms for PTSD and TBI overlap.

Interventions

The EFT intervention must be delivered with fidelity to the standard text used in virtually all clinical trials. The EFT Manual, currently in its fourth edition (Church, 2018). Besides manualization, as many other CONSORT standards as possible should be used.

The therapist must have undergone training in Clinical EFT, and treatment fidelity should be monitored by the perusal of the therapist's written notes by investigators. This ensures that all Clinical EFT standards are met (ClinicalEFT.com).

The description of the WET protocol does meet conventional standards, including stating the manualized protocol used, and clinician training. However, similar fidelity checks are recommended.

Adverse event reporting procedures are satisfactory.

Exploratory Outcomes

A large number of supplemental questionnaires is proposed. In many studies, a requirement that participants spend hours filling out forms presents a barrier to participation.
While this information provides a rich and multidimensional picture of participant wellbeing, the investigators might review whether or not this large number of assessments resulted in participant attrition in the pilot study. If it did, this approach can be revisited.

**Sample Size**

The sample size of 120 is just barely sufficient to detect difference in 3 groups of 38, accounting for dropouts. The investigators might consider adding another 15 to 20 subjects to the study to reduce the possibility that dropout numbers or noncompliance rates will reduce the final sample size below the desired level.

**Allocation**

The randomization procedure is appropriate.

**Blinding**

See earlier comments.

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**GENERAL COMMENTS**

General comments

The authors describe an ambitious study on EFT as a psychological treatment for PTSD. Novel interventions with good efficacy and compliance/low dropout rates are needed in the field. By utilizing a three-arm RCT the authors will be able to compare EFT to WL, WET, an intervention of similar duration with EFT, to WL as well as to compare directly EFT to WET. The figures are illustrative of the recruitment process, intervention delivery and follow-up. It is unclear how the healthy population will be used for the objectives of this study. Another issue is that throughout the paper the final follow-up occurs at 12 weeks, but in the recruitment figure there is a close-out at 24 weeks, when all the outcome measures collected also at week 12 are collected. Taking into consideration that the participants initially assigned to WL will receive EFT after 12 weeks, I wonder about the rationale for having data collected at week 24. If it is to obtain longer follow-up data for the active interventions, this should be stated as an objective.

**Introduction**

Lines 82-87: The issue of dropout from psychotherapies for PTSD is very relevant. The authors write “…a lack of buy-in to treatment and too stressful course, which were mostly related to uncomfortable exposure to the past.” Of course, the uncomfortable exposure to past traumatic events makes the course of the treatment stressful and can negatively influence the patient’s motivation to go through the whole treatment course. Are there any other reasons for the high dropout rate?

What are the dropout rates for other psychotherapeutic interventions? Are the dropout rates for PTSD treatment higher than for other interventions?
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 b. In this paragraph, imaging and biomarkers are mentioned for the diagnosis and prognosis of PTSD treatment as well as for understanding the underlying mechanisms. If the aim of this study is to incorporate imaging to explore the underlying mechanisms as stated in the end of the paragraph, the authors should focus on the literature describing the underlying mechanisms of different psychotherapies for PTSD as ascertained by imaging techniques. |
| 114-115 | I recommend changing “…and seeking predictive factors that affect the response to PTSD treatments” to “…and seeking predictive factors for the response to PTSD treatments”. |
|      | As a general comment in the introduction, the authors can consider mentioning some measures of efficacy for the different treatments discussed, for example, effect sizes for the WET intervention which is what the EFT intervention will be compared to in the non-inferiority study, as well as how the effect size of the |
WET intervention is related to the ones for the interventions with the best evidence (eg exposure therapy and EMDR).

Objectives
I really miss the objective of measuring compliance and drop-out rates, as the introduction has illustrated this as a problem with existing treatments.

Line 132: The authors write: “…proportion of loss of PTSD diagnosis and full remission of PTSD after the intervention”. Isn’t the “loss of PTSD diagnosis” the same as “full remission”? In that case you can omit this phrase. Or do the authors mean “partial remission” or “response”?

Lines 138-141:
The explorative purpose defined here is not the same as in lines 123-124.

Maybe the authors want to explore all three alternatives: biomarkers (blood-based, imaging- or videos-based) for the i) diagnosis of PTSD at baseline – separate people with the diagnosis from those without (in which case I also understand the utility of the healthy population), ii) for the prognosis with treatment – can we use biomarkers to identify people at higher probability for successful treatment? and iii) to understand the underlying mechanisms – for those people with successful treatment do we see any imaging patterns that can inform us about the underlying mechanisms? If this is the case then all three should be stated. But now I think the authors refer to these different objectives interchangeably.

The “various questionnaires related to gastrointestinal symptoms, empathy, and Korean medicine patterns” are mentioned for the first time here, without providing any rational for their relevance in the introduction.

Eligibility criteria
• Why only women?
• What does it mean “regular visits once a week for 6 weeks” ? Now, I am uncertain if you want to study compliance and dropout rates, as this is not stated in the objective, but if you do, then this inclusion criteria introduces a selection bias. Those women will be more prone to completing the study won’t they?
• Could you define in more detail what “risk of suicide” means?
• How are you going to assess cognitive impairment?
• What about having previously received psychotherapy for PTSD? Is this an exclusion criterium?
• “women who do not use medically acceptable contraception during the study period; those determined as unsuitable by the investigators.” This should be defined more clearly and there are some ethical implications if the women feel they cannot become pregnant during the study. How are they informed about this?
• There is a long list of exclusion criteria for a study with a psychotherapeutic intervention. Several but not all exclusion criteria are easy to understand. I think the readers would appreciate the authors’ rationale for the exclusion criteria relating to eg. infections, antibiotics, vaccinations, neurological and systemic diseases etc
• Healthy controls:
There is no objectives described including analyses with the healthy controls.

Where and how are the healthy controls going to be recruited?

Interventions

- Line 192-193: I think that it is not totally clear for the non-psychotherapist reader what the procedures mean. Could you please clarify?
- Line 196: A short description of cognitive reframing would also be appreciated.
- Lines 199-202: How big the improvement with WET was?
- Line 204: what is the WET script?
- Line 218: “participants who do not meet the inclusion and exclusion criteria,” Do you mean participants who stop meeting inclusion criteria?
- Line 219: How are “the serious adverse events” defined and followed up in this study?
- Line 222: “participants whose compliance with the intervention is <70%”- How are you going to assess this while the study is ongoing?
- Lines 233-237: Please define “loss of PTSD diagnosis”.
- Who is going to deliver the interventions? Will there be any training for the people delivering the interventions?

Outcomes

Exploratory outcomes

- Line 247: “emotions of funny”, please clarify/rephrase as necessary
- Line 248: “…and the facial expressions of participants during the tasks will be recorded and analyzed.”. How will the videos be analysed? A very short description is needed.
- Lines: 249. The pain threshold is mentioned for the first time here. It should be mentioned earlier as well, preferably with some introduction of its relevance for the current project.

Sample size

- Line 258: “We estimated that EFT would have an effect size similar to that of EMDR”. Here you could also cite the work by Karatzias (number 14 in your reference list).

I recommend including a power analysis also for the non-inferiority objective, even if the non-inferiority margin will be definitely defined later.

Recruitment

The authors should provide the start date for the study if ongoing, and the expected end date.

Blinding

- Line 288: “safety will be evaluated …” Which are the safety outcomes to assess. These should be described earlier as well in the objectives and outcome measures.
- Line 290: “Visits for interventions (3–7) and assessment (2, 8, and 9) will be separated.” What assessment will be made in week 9? There is also an assessment at week 12, who is the assessor at that timepoint?

Data collection
The authors utilize both clinician-administered tools (CAPS-5) and self-reported validated instruments such as the BDI-II. The reader would appreciate that this is clearly mentioned throughout the manuscript, as well as details on the collection of self-reported data, when and how are the collected?

Data management
Line 307: Could you please clarify what the “source document data” is?

Statistical methods
Line 320-321: “Safety assessment”: this is not described in the objectives and outcome measures
Line 334: “The lower the 95% CI of the mean difference between two groups will be M.” Do the authors mean the lower limit of the 95% of the mean difference…”?

Harms
Lines 370-371: ” 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”. Lines 412: “The occurrence of adverse events will be assessed at every visit, and the required treatment and observation will be applied until the symptoms disappear”.

However, the authors also state in lines 289-290 “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.”

I wonder thus how will the adverse events be identified, at which visits, how (which questionnaires) and by whom (independent assessors or the clinicians delivering the interventions).

VERSION 1 – AUTHOR RESPONSE

Response to Comments from Reviewer 1

Comment 1 (Abstract):
1-1) In the Introduction, the authors refer to EFT as a “meridian-based psychotherapy” While this is correct, it is preferable to use “acupressure-based” since many readers will not understand what acupuncture meridians are till they are explained in the Introduction.
1-2) Also in the Introduction, they refer to “The emotional freedom technique." Emotional Freedom Techniques is always plural, because there are 48 of them, viewable at ClinicalEFT.com.
1-3) In the Introduction the authors also state that "the clinical evidence and underlying mechanisms are unknown.” However, a decade of research has identified mechanisms such as attenuation of the fear response in the brain (in many MRI and EEG studies), epigenetic changes, hormonal shifts, and regulation of biomarkers like heart rate and immunoglobulins. So the mechanisms are hardly unknown. Similarly, with over 200 clinical trials, and many meta-analyses, the clinical evidence is not unknown.

Methods. The three arm design, with WET and Wait List, is a robust design. The comparator conditions are appropriate. The large N is to be commended, with qualifications as noted below. A further strength of the design is obtaining a categorical diagnosis of PTSD using the CAPS scale in addition to self-report.

Response 1:
Thank you for your thoughtful suggestion to our abstract. We have made the following changes:

1-1) We have revised the introduction to refer to EFT as an “acupuncture-based psychotherapy.”
1-2) We have corrected the wording to “Emotional Freedom Techniques” to reflect the plurality of the techniques.
1-3) We have revised the statement on the clinical evidence and underlying mechanisms of EFT to acknowledge the previous extensive research that has been conducted in these areas.

Comment 2 (Strengths and Limitations Section):
2-1) This section makes its points effectively. The last one, that participants cannot be blinded, could be reconsidered. Participants can be effectively blinded if they are not informed that there is a second treatment group.
2-2) It is also possible to blind clinicians by concealing the existence of a second treatment from them, though this is challenging if they work in the same institution.

Response 2:
2-1) Thank you for your constructive comments. With regard to your comment on blinding, we agree that blinding participants and clinicians using suggested methods will improve the quality of the trial and reduce potential bias. However, in the context of our study, blinding participants is not feasible due to the presence of a waiting list control group.
2-2) Regarding blinding clinicians, we understand that concealing the existence of a second treatment group could be a possible solution. However, due to the composition of our research team, it would not be possible to completely conceal the existence of a second treatment group from clinicians. We have slightly revised the Strengths and Limitations section of the manuscript.

Comment 3 (Introduction):
3-1) Repeat of above comments on “The emotional freedom technique” and “meridian-based psychotherapy”
3-2) The literature review should include the meta-analysis of EFT for PTSD (Sebastian & Nelms 2016) and the systematic review of EFT that included more recent PTSD research (Church, Stapleton, Vasudevan & O’Keefe, 2022).

Response 3:
3-1) Thank you for the comments. We have revised the introduction to refer to EFT as an “acupuncture-based psychotherapy.”
3-2) The introduction has been revised to reflect the findings of recent systematic reviews.

Comment 4 (Objectives):
The assessments are appropriate. A one-item insomnia assessment, the ISI, is mentioned later, and should be added to this section. Adding a one-item pain assessment such as the Pain Rating Scale would be useful.
The eligibility criteria are appropriate, in particular the inclusion of patients with mild TBI, since the symptoms for PTSD and TBI overlap.

Response 4:
Thank you for your helpful comments. We have incorporated the Insomnia Severity Index (ISI) into our objective section as you recommended. As for the Pain Rating Scale, we understand its importance; however, we have decided not to include it due to the high number of outcomes already included in this study.

Comment 5 (Interventions):
The EFT intervention must be delivered with fidelity to the standard text used in virtually all clinical trials, The EFT Manual, currently in its fourth edition (Church, 2018). Besides manualization, as many other CONSORT standards as possible should be used.

5-2) The therapist must have undergone training in Clinical EFT, and treatment fidelity should be monitored by the perusal of the therapist’s written notes by investigators. This ensures that all Clinical EFT standards are met (ClinicalEFT.com).

5-3) The description of the WET protocol does meet conventional standards, including stating the manualized protocol used, and clinician training. However, similar fidelity checks are recommended. Adverse event reporting procedures are satisfactory.

Response 5:

5-1) We agree with the comment and have revised the manuscript to specify that the EFT intervention will be delivered following the EFT Manual (4th edition).

5-2) We have revised the manuscript to include information on how treatment fidelity will be monitored. The therapists will undergo training in Clinical EFT and the treatment fidelity will be monitored by the perusal of the therapist’s written notes by investigators.

5-3) We have revised the manuscript to specify that fidelity checks will be conducted for both EFT and WET interventions.

Comment 6 (Exploratory Outcomes):
A large number of supplemental questionnaires is proposed. In many studies, a requirement that participants spend hours filling out forms presents a barrier to participation. While this information provides a rich and multidimensional picture of participant wellbeing, the investigators might review whether or not this large number of assessments resulted in participant attrition in the pilot study. If it did, this approach can be revisited.

Response 6:
We agree that participant burden is a concern, and we have carefully considered your comments and the response of participants who have already enrolled in our study. After reviewing our protocol and taking into account the burden on participants, we have decided to remove most of the supplemental questionnaires in our study. We believe this will help to reduce the burden on participants while still obtaining valuable data for our study.

Comment 7 (Sample size):
The sample size of 120 is just barely sufficient to detect difference in 3 groups of 38, accounting for dropouts. The investigators might consider adding another 15 to 20 subjects to the study to reduce the possibility that dropout numbers or noncompliance rates will reduce the final sample size below the desired level.

Response 7:
We agree with your concern regarding the sample size of 120 being just barely sufficient. However, due to limited time and research funds, we have set the number of participants to 120. We will make every effort to minimize the dropout rate. Additionally, we will consider increasing the sample size in the event that the dropout rate is higher than expected.

Response to Comments from Reviewer 2
Comment 1 (General):
1-1) The authors describe an ambitious study on EFT as a psychological treatment for PTSD. Novel interventions with good efficacy and compliance/low dropout rates are needed in the field. By utilizing a three-arm RCT the authors will be able to compare EFT to WL, WET, an intervention of similar duration with EFT, to WL as well as to compare directly EFT to WET. The figures are
illustrative of the recruitment process, intervention delivery and follow-up. It is unclear how the healthy population will be used for the objectives of this study.

1-2) Another issue is that throughout the paper the final follow-up occurs at 12 weeks, but in the recruitment figure there is a close-out at 24 weeks, when all the outcome measures collected also at week 12 are collected. Taking into consideration that the participants initially assigned to WL will receive EFT after 12 weeks, I wonder about the rationale for having data collected at week 24. If it is to obtain longer follow-up data for the active interventions, this should be stated as an objective.

Response 1:
1-1) Thank you for your insightful comments. We have added a comparison of baseline characteristics between PTSD patients and healthy controls to explore the biomarkers of PTSD diagnosis. The exploratory objectives are specified in our response to comment 3.
1-2) Regarding the data collection at week 24, it will be conducted as a supplementary measure. The primary outcome for the study is CAPS-5, which is assessed at baseline (week 0), post-treatment (week 6), and follow-up (week 12). The data collection at week 24 will only include a self-rated questionnaire and cannot be compared between groups, as the participants in the WL group will receive EFT after 12 weeks. The data collected at week 24 will be limitedly analyzed within each group.

Comment 2 (Introduction):
Lines 82-87: The issue of dropout from psychotherapies for PTSD is very relevant. The authors write “…a lack of buy-in to treatment and too stressful course, which were mostly related to uncomfortable exposure to the past.” Of course, the uncomfortable exposure to past traumatic events makes the course of the treatment stressful and can negatively influence the patient’s motivation to go through the whole treatment course. Are there any other reasons for the high dropout rate? What are the dropout rates for other psychotherapeutic interventions? Are the dropout rates for PTSD treatment higher than for other interventions? What kind of improvement can one expect for better compliance/fewer dropouts?
The authors continue writing “Thus, effective and efficient therapy is required to increase compliance and remission in patients with PTSD.” The authors have illustrated the need for interventions with lower dropout rates but they haven’t formulated a problem related to the efficacy of already existing therapies, eg exposure therapy. It would be clearer for the reader if this is further elaborated and motivated.
It is also relevant to discuss the efficacy and compliance together. A new intervention with better compliance would ideally be at least as efficacious as the established intervention with the problematic dropout rates. It is also relevant to discuss the efficacy and compliance together. A new intervention with better compliance would ideally be at least as efficacious as the established intervention with the problematic dropout rates.
Line 88: I think it would be beneficial for the readers to provide some more information on how the EFT is conducted.
Line 101-103. I would suggest that the authors consider moving this information on recommended treatments earlier in the introduction, eg in line 79.
Line 105: Why is it a limitation that the previous studies used “symptom-related parameters to assess efficacy”? Can the authors explain? PTSD symptoms is the main outcome measurement for this study as well.
Line 107-110: Very interesting with the feasibility study. If it is published, please cite the study. If not, please mention more concrete results about the improvement, compliance and dropouts.
Line 111: “as it is a short-term therapy that is adequate for comparison with 5-session of EFT”. The duration of EFT treatment in relation to that of other treatments, ie exposure therapy, is also an interesting point the authors might want to consider mentioning as an advantage against other interventions as well as a factor for better compliance and fewer dropouts.
Line 113-124:
a. The authors make a short introduction to the field of imaging in PTSD. However, an introduction to blood-based biomarkers and facial expressions, which are going to be collected and analysed in the study, is missing.
b. In this paragraph, imaging and biomarkers are mentioned for the diagnosis and prognosis of PTSD treatment as well as for understanding the underlying mechanisms. If the aim of this study is to incorporate imaging to explore the underlying mechanisms as stated in the end of the paragraph, the authors should focus on the literature describing the underlying mechanisms of different psychotherapies for PTSD as ascertained by imaging techniques.

Line 114-115: I recommend changing “…and seeking predictive factors that affect the response to PTSD treatments” to “…and seeking predictive factors for the response to PTSD treatments”. As a general comment in the introduction, the authors can consider mentioning some measures of efficacy for the different treatments discussed, for example, effect sizes for the WET intervention which is what the EFT intervention will be compared to in the non-inferiority study, as well as how the effect size of the WET intervention is related to the ones for the interventions with the best evidence (e.g. exposure therapy and EMDR).

Response 2:
Thank you for your valuable comments and suggestions. We have revised the introduction. Regarding some of your valuable comments, we located some information about the EFT procedure, the results of the feasibility trial, and WET to the method section to avoid repetition in the introduction. Additionally, we would like to inform you that the manuscript of the previous feasibility trial is currently under review by a journal. We have included more information about the results in the method section under the Interventions subsection.

Comment 3 (Objectives):
3-1) I really miss the objective of measuring compliance and drop-out rates, as the introduction has illustrated this as a problem with existing treatments.
3-2) Line 132: The authors write: “…proportion of loss of PTSD diagnosis and full remission of PTSD after the intervention”. Isn’t the “loss of PTSD diagnosis” the same as “full remission”? In that case you can omit this phrase. Or do the authors mean “partial remission” or “response”?
3-3) Lines 138-141: The explorative purpose defined here is not the same as in lines 123-124. Maybe the authors want to explore all three alternatives: biomarkers (blood-based, imaging- or videos-based) for the i) diagnosis of PTSD at baseline – separate people with the diagnosis from those without (in which case I also understand the utility of the healthy population), ii) for the prognosis with treatment – can we use biomarkers to identify people at higher probability for successful treatment? and iii) to understand the underlying mechanisms – for those people with successful treatment do we see any imaging patterns that can inform us about the underlying mechanisms? If this is the case then all three should be stated. But now I think the authors refer to these different objectives interchangeably.
3-4) The “various questionnaires related to gastrointestinal symptoms, empathy, and Korean medicine patterns” are mentioned for the first time here, without providing any rational for their relevance in the introduction.

Response 3:
Thank you for your insightful comments and valuable suggestions.
3-1) We have revised the manuscript to include measuring compliance and drop-out rates as an additional objective, as suggested.
3-2) We agree that the phrase "loss of PTSD diagnosis" may have been unclear and could be misinterpreted as being the same as "full remission." To clarify, we have added the definition of "loss of PTSD diagnosis" as no longer meeting the criteria for PTSD.
Thank you for your insightful comments. We have revised the exploratory objective section to more specifically state the three objectives.

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.

We have removed those various questionnaires to reduce the participant burden.

Comment 4 (Eligibility criteria):

4-1) Why only women?
4-2) What does it mean “regular visits once a week for 6 weeks”? Now, I am uncertain if you want to study compliance and dropout rates, as this is not stated in the objective, but if you do, then this inclusion criteria introduces a selection bias. Those women will be more prone to completing the study won’t they?
4-3) Could you define in more detail what “risk of suicide” means?
4-4) How are you going to assess cognitive impairment?
4-5) What about having previously received psychotherapy for PTSD? Is this an exclusion criterion?
4-6) “women who do not use medically acceptable contraception during the study period; those determined as unsuitable by the investigators.” This should be defined more clearly and there are some ethical implications if the women feel they cannot become pregnant during the study. How are they informed about this?
4-7) There is a long list of exclusion criteria for a study with a psychotherapeutic intervention. Several but not all exclusion criteria are easy to understand. I think the readers would appreciate the authors’ rationale for the exclusion criteria relating to eg. infections, antibiotics, vaccinations, neurological and systemic diseases etc
4-8) Healthy controls: There is no objectives described including analyses with the healthy controls. Where and how are the healthy controls going to be recruited?

Response 4:

Thank you for providing us with valuable feedback.

4-1) Originally, we planned to only include women to increase the homogeneity among participants. However, due to the difficulty of recruiting participants, we changed that inclusion criteria to include both sexes.
4-2) Regarding “regular visits once a week for 6 weeks,” there are some people who cannot do regular visits due to moving plans or long distances from the site, not because of compliance issues with the intervention. Those criteria intended to exclude those kinds of participants. We revised the sentence to clarify. (“willing to attend weekly visits for 6 weeks”)
4-3) Risk of suicide will be assessed using C-SSRS. We added the details.
4-4) Originally, we planned to exclude participants who received previous psychotherapy for PTSD within 6 months. However, we could not enroll participants with those criteria because most participants with PTSD had recently received psychotherapy for PTSD. As a result, we will enroll participants if they are not receiving current psychotherapy. Participants with past experience of psychotherapy can be included. Previous experience of psychotherapy will be carefully checked and recorded in the screening process.
4-5) We do not think the intervention in this study has a risk to participants being pregnant, but intended to exclude those participants. If someone has a plan to become pregnant within the study period, she will be excluded, and the enrolled women will be recommended to maintain contraception to avoid ethical issues of conducting clinical trials on pregnant women.
Antipsychotics, antidepressants, benzodiazepines, and sleep medications can affect the results of the study. Systemic steroid, antibiotics, and vaccination were included in the exclusion criteria because of the exploratory objectives in this study. We plan to analyze inflammatory biomarkers in collected blood samples of participants, which can be affected by those medications.

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.

Comment 5 (Interventions):

5-1) Line 192-193: I think that it is not totally clear for the non-psychotherapist reader what the procedures mean. Could you please clarify?
5-2) Line 196. A short description of cognitive reframing would also be appreciated.
5-3) Lines 199-202. How big the improvement with WET was?
5-4) Line 204: what is the WET script?
5-5) Line 218: “participants who do not meet the inclusion and exclusion criteria,” Do you mean participants who stop meeting inclusion criteria?
5-6) Line 219: How are “the serious adverse events” defined and followed up in this study?
5-7) Line 222: “participants whose compliance with the intervention is <70%”- How are you going to assess this while the study is ongoing?
5-8) Lines 233-237. Please define “loss of PTSD diagnosis”.
5-9) Who is going to deliver the interventions? Will there be any training for the people delivering the interventions?

Response 5:
Thank you for your valuable comments and suggestion.

5-1) We have revised the “Intervention” section to provide a more detailed explanation of the procedures involved in EFT.
5-2) We have updated the “Intervention” section to include a brief description of cognitive reframing.

(lines 208-216) 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.

5-3) We have added information on the effect size of WET treatment in the revised “Intervention” section. The study showed that the severity of PTSD symptoms was alleviated with a large effect size (partial η²: 0.524 for PCL-5) after five sessions of WET.
5-4) We have added information that the WET script was developed by Sloan et al. and that it provides standard instructions for conducting WET.

5-5) We apologize for the unclear phrasing in the original manuscript. We meant that participants who are found to be not meeting the inclusion and exclusion criteria will be discontinued from the treatment and eliminated from the study. We have revised the manuscript to reflect this more clearly.

5-6) We define serious adverse events as those that are life-threatening, result in hospitalization, or lead to death. We have updated the manuscript to reflect this more specifically.

(lines) participants with serious adverse events (death, life-threatening, or hospitalization due to adverse events).

5-7) We apologize for including the criterion “participants whose compliance with the intervention is <70%” in the original manuscript. We have removed this criterion from the revised manuscript, as it
is not part of our protocol. Participants who do not comply with the intervention at a rate of less than 70% will not be discontinued from the study. They will be excluded from the per protocol analysis. If possible, the intervention and assessment will be completed for these participants.

5-8) We have added the definition of “loss of PTSD diagnosis” as no longer meeting the criteria for PTSD.

5-9) We have revised the manuscript to specify that the qualified therapists who will deliver the interventions have completed exposure-based treatment and Clinical EFT or WET protocol training. This information has been added to the revised manuscript.

Comment 6 (Outcomes):
Exploratory outcomes
6-1) Line 247: “emotions of funny”, please clarify/rephrase as necessary.
6-2) Line 248: “…and the facial expressions of participants during the tasks will be recorded and analyzed.”. How will the videos be analysed? A very short description is needed.
6-3) Lines: 249. The pain threshold is mentioned for the first time here. It should be mentioned earlier as well, preferably with some introduction of its relevance for the current project.

Response 6:
Thank you for your comments and suggestions on our manuscript.
6-1) We have revised it to “emotions of joy” for clarity.
6-2) The facial expression analysis will be conducted using iMotions software.
6-3) We appreciate your suggestion to mention the pain threshold earlier in the manuscript. However, we have removed pain threshold measurement from our exploratory outcomes to reduce the burden on participants.

Comment 7 (Sample size):
7-1) Line 258: “We estimated that EFT would have an effect size similar to that of EMDR”. Here you could also cite the work by Karatzias (number 14 in your reference list).
7-2) I recommend including a power analysis also for the non-inferiority objective, even if the non-inferiority margin will be definitely defined later.

Response 7:
7-1) Thank you for your suggestion. We have cited the work by Karatzias to the sentence.
7-2) We appreciate your suggestion and agree that including a power analysis for the non-inferiority objective is important. However, as the non-inferiority margin will be defined later, it is difficult to perform a power analysis at this stage. Additionally, there is insufficient information to perform a power analysis for non-inferiority, and it would require a lot of assumptions. Assuming a significance level (alpha) of 0.05, power (beta) of 0.2, standard deviation of 17, mean difference of 0, and a non-inferiority margin of 10, the required sample size is 36 per group without accounting for dropout rates.

Comment 8 (Recruitment):
The authors should provide the start date for the study if ongoing, and the expected end date.

Response 8:
Thank you for your valuable feedback. 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. We have now included this information in the revised manuscript.

Comment 9 (Blinding):
9-1) Line 288: “safety will be evaluated …”. Which are the safety outcomes to assess. These should be described earlier as well in the objectives and outcome measures.
9-2) Line 290: “Visits for interventions (3–7) and assessment (2, 8, and 9) will be separated.” What assessment will be made in week 9? There is also an assessment at week 12, who is the assessor at that timepoint?

Response 9:
9-1) Thank you for your valuable comments. We added a safety outcome section in the method to describe the safety outcomes in more detail.
9-2) Visit 2 (week 0) is for the assessment before the intervention, visit 8 (week 6) is for the assessment after the intervention, and visit 9 (week 12) is for the assessment during the follow-up period. The primary outcome, CAPS-5, will be evaluated by the blinded assessors in those three assessment visits. In visit 10 (week 24), it is an additional online assessment, and only self-rating questionnaires will be completed. We hope this clarifies the assessment schedule.

Comment 10 (Data collection):
The authors utilize both clinician-administered tools (CAPS-5) and self-reported validated instruments such as the BDI-II. The reader would appreciate that this is clearly mentioned throughout the manuscript, as well as details on the collection of self-reported data, when and how are the collected?

Response 10:
Thank you for the comments. We revised the manuscript to clearly mention the use of clinician-administered tool and self-reported instruments. In addition, we summarized the data collection schedules for the study in Figures 1 and 2.

Comment 11 (Data management):
Line 307: Could you please clarify what the “source document data” is?

Response 11:
Thank you for your comments. To clarify, we revised the sentence. Data in source documents refers to data obtained from predefined source documents such as assessment sheets completed by investigators, questionnaires filled out by participants, and electronic medical records.

Comment 12 (Statistical methods):
12-1) Line 320-321: “Safety assessment”: this is not described in the objectives and outcome measures
12-2) Line 334: “The lower the 95% CI of the mean difference between two groups will be M.” Do the authors mean the lower limit of the 95% of the mean difference…”?

Response 12:
Thank you for your valuable comments.
12-1) We have added safety assessment in the objectives and outcome measures.
12-2) We have changed to the lower limit of the 95% of the mean difference. Thank you.

Comment 13 (Harms):
Lines 370-371: “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”.
Lines 412: “The occurrence of adverse events will be assessed at every visit, and the required treatment and observation will be applied until the symptoms disappear”.
However, the authors also state in lines 289-290 “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.”
I wonder thus how will the adverse events be identified, at which visits, how (which questionnaires) and by whom (independent assessors or the clinicians delivering the interventions).
Response 13:
Thank you for your valuable comments. To clarify, the collection and assessment of adverse events will be conducted at every visit. The investigators conducting these assessments will differ depending on the visit. During the Visits for interventions (visit 3–7), the clinicians delivering the interventions will inquire about any adverse events that occurred. At the visits for assessment (2, 8, and 9), independent blinded assessors will collect and assess the adverse events, as well as assess the risk of suicide using C-SSRS. We have revised the manuscript accordingly to reflect this.

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<tr>
<th>REVIEWER</th>
<th>Church, Dawson</th>
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<td></td>
<td>National Institute for Integrative Healthcare</td>
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<td>REVIEW RETURNED</td>
<td>12-Apr-2023</td>
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GENERAL COMMENTS None.

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<th>Papadopoulos, Fotios C.</th>
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<td>REVIEW RETURNED</td>
<td>08-May-2023</td>
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GENERAL COMMENTS Review for "Emotional freedom technique versus written exposure therapy versus waiting list for post-traumatic stress disorder: protocol for a randomized clinical MRI study"

Thank you for the revision of the article which is much improved.

After reading your replies to my comments, I have the following major concerns and minor comments.

Major concerns:

1. You wrote “Originally, we planned to exclude participants who received previous psychotherapy for PTSD within 6 months. However, we could not enroll participants with these criteria because most participants with PTSD had recently received psychotherapy for PTSD. As a result, we will enroll participants if they are not receiving current psychotherapy. Participants with past experience of psychotherapy can be included. Previous experience of psychotherapy will be carefully checked and recorded in the screening process.”

This is a very important point which must be stated in the paper. I strongly encourage the authors to reflect on how this selection of patients influences the trial and how generalizable the results will be.

What kind of psychological treatment will most of the participants have received before the trial? If they meet the inclusion criteria we can conclude that the previous treatment did not have a sufficient effect and they meet the criteria for a PTSD diagnosis. Are we talking then about a
population with “treatment-resistant PTSD” and if yes, what are the reasons for that? More severe trauma?

2. In the exclusion criteria it is stated “pregnant or lactating women; women who do not use medically acceptable contraception during the study period; those determined as unsuitable by the investigators.” The authors replied to my previous comment with this clarification “We do not think the intervention in this study has a risk to participants being pregnant, but intended to exclude those participants. If someone has a plan to become pregnant within the study period, she will be excluded, and the enrolled women will be recommended to maintain contraception to avoid ethical issues of conducting clinical trials on pregnant women.”

Here we have different ethical issues, conducting clinical trials on pregnant women is one, but still one can argue that the psychological intervention is safe. The other ethical issue is to recommend contraception and how to do this recommendation, will the women feel obliged to adhere to that recommendation?

One could just exclude pregnant women at entry. Even if a woman becomes pregnant very soon after enrolling to the study she would have time to complete the 12 weeks or 24 weeks up to midpregnancy.

Another issue is what kind of contraception that is accepted. Is it contraception pills the authors call “medically acceptable contraception”? Starting contraception pills for the study among women participants may be problematic as one introduces a medical treatment, with known effects on fear extinction in combination with the psychotherapeutic intervention, which will make it difficult to assess the effect of the psychotherapeutic intervention for women.

All in all, I don’t think it is justifiable to exclude non-pregnant women not on contraceptives or to make them feel they have to start on the pill; not from an ethical perspective or a scientific/neurobiological one.

3. In the Criteria for discontinuing or modifying allocated interventions it is mentioned: “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, …”

Despite the clarification by the authors, I still need help understanding. Will the inclusion and exclusion criteria be assessed in every visit or assessment? But how will this work with the inclusion criterion of PTSD? Will people no
longer meeting the criteria for PTSD be stopped from treatment and eliminated from the study? Will people developing an infection be stopped from the study?

Minor concerns

1. Loss of PTSD diagnosis vs remission. Thank you for your clarifications. I still find it a bit confusing. You may consider naming criteria-based and symptom-based remission. This is because remission can also be defined as when one fulfills less than necessary number of criteria.
2. Thank you for providing the power analysis, I suggest that you will include it also in the paper, as it supports the size for your three groups!
4. Line 160 (and in other places): “potential biomarkers and predictors”. Biomarkers are also predictors. Maybe rephrase to “potential biomarkers and other predictors”.

VERSION 2 – AUTHOR RESPONSE

Response to Comments from Reviewer 2

Comment 1:

You wrote “Originally, we planned to exclude participants who received previous psychotherapy for PTSD within 6 months. However, we could not enroll participants with those criteria because most participants with PTSD had recently received psychotherapy for PTSD. As a result, we will enroll participants if they are not receiving current psychotherapy. Participants with past experience of psychotherapy can be included. Previous experience of psychotherapy will be carefully checked and recorded in the screening process. “This is a very important point which must be stated in the paper. I strongly encourage the authors to reflect on how this selection of patients influences the trial and how generalizable the results will be. What kind of psychological treatment will most of the participants have received before the trial? If they meet the inclusion criteria we can conclude that the previous treatment did not have a sufficient effect and they meet the criteria for a PTSD diagnosis. Are we talking then about a population with “treatment-resistant PTSD” and if yes, what are the reasons for that? More severe trauma?

Response 1:

Thank you for your thoughtful suggestions. We have incorporated the revised exclusion criteria and the background behind these changes into our paper.

Furthermore, the information regarding previously received psychotherapy that we are collecting includes the type of psychotherapy (such as CBT, PE, EMDR, CPT, NET, other, or unknown) and the duration of psychotherapy. In one reference, "treatment-resistant PTSD" was defined as meeting PTSD criteria despite having previously undergone at least 6 months of psychotherapy and 3 months of treatment with an SSRI (Oehen, 2013, Journal of Psychopharmacology, doi: 10.1177/0269881112464827). In another study, "antidepressant-resistant PTSD" was defined as the persistence of PTSD symptoms despite at least 2 adequate SRI treatments (Krystal, 2011, JAMA, doi: 10.1001/jama.2011.1080). In our study, we anticipate that we will be able to observe the proportion of participants with treatment-resistant PTSD among enrolled participants, based on the collected information on psychotherapy history, as well as evaluate their response to EFT or WET treatments.
Exclusion criteria will be (...) 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.) (...)

Comment 2:

In the exclusion criteria it is stated “pregnant or lactating women; women who do not use medically acceptable contraception during the study period; those determined as unsuitable by the investigators.” The authors replied to my previous comment with this clarification “We do not think the intervention in this study has a risk to participants being pregnant, but intended to exclude those participants. If someone has a plan to become pregnant within the study period, she will be excluded, and the enrolled women will be recommended to maintain contraception to avoid ethical issues of conducting clinical trials on pregnant women.” Here we have different ethical issues, conducting clinical trials on pregnant women is one, but still one can argue that the psychological intervention is safe. The other ethical issue is to recommend contraception and how to do this recommendation, will the women feel obliged to adhere to that recommendation? One could just exclude pregnant women at entry. Even if a woman becomes pregnant very soon after enrolling to the study she would have time to complete the 12 weeks or 24 weeks up to midpregnancy. Another issue is what kind of contraception that is accepted. Is it contraception pills the authors call “medically acceptable contraception”? Starting contraception pills for the study among women participants may be problematic as one introduces a medical treatment, with known effects on fear extinction in combination with the psychotherapeutic intervention, which will make it difficult to assess the effect of the psychotherapeutic intervention for women. All in all, I don’t think it is justifiable to exclude non-pregnant women not on contraceptives or to make them feel they have to start on the pill; not from an ethical perspective or a scientific/neurobiological one.

Response 2:

Thank you for your valuable comment. Your feedback has prompted us to reassess the ethical considerations surrounding the inclusion of pregnant women in our psychological intervention clinical study. Given that this study does not involve new drugs or invasive devices, we agree that it is not necessary to exclude pregnant women from participation. However, due to various challenges in modifying the current protocol of our ongoing study, we have decided to proceed with the study as planned.

In response to the concerns you raised, we fully acknowledge that it would be ethically problematic if women participating in the study felt compelled to take contraceptive pills. To address this, we have provided explicit details in the protocol regarding what constitutes “medically acceptable contraception.” These methods include barrier methods, combined oral contraceptives, contraceptive implant, contraceptive injection, intrauterine devices, and personal or partner’s sterilization. Since barrier methods are encompassed within the accepted contraceptive options, women participating in the study are not required to take contraceptive pills. We will ensure that all women involved in the study are sufficiently informed about the recommended contraceptive methods. Additionally, we have included the definition of “medically acceptable contraception” in the manuscript to provide further clarification on this matter.

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
Comment 3:

In the Criteria for discontinuing or modifying allocated interventions it is mentioned: “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, ...” Despite the clarification by the authors, I still need help understanding. Will the inclusion and exclusion criteria be assessed in every visit or assessment? But how will this work with the inclusion criterion of PTSD? Will people no longer meeting the criteria for PTSD be stopped from treatment and eliminated from the study? Will people developing an infection be stopped from the study?

Response 3:

Thank you for your valuable comments. To clarify, we have revised the sentence regarding the criteria for discontinuing or modifying allocated interventions as follows: "participants who are found to have not met the inclusion and exclusion criteria at the screening period due to an error."

The inclusion and exclusion criteria will be assessed during the screening process, which occurs before the participant’s enrollment in the study, and will be not reassessed during subsequent visits.

Comment 4:

Loss of PTSD diagnosis vs remission. Thank you for your clarifications. I still find it a bit confusing. You may consider naming criteria-based and symptom-based remission. This is because remission can also be defined as when one fulfills less than necessary number of criteria.

Response 4:

Thank you for your valuable suggestion, which can provide a clearer understanding for readers. We have revised the terminology from “loss of PTSD diagnosis vs remission” to “criteria-based vs symptom-based remission.”

Comment 5:

Thank you for providing the power analysis, I suggest that you will include it also in the paper, as it supports the size for your three groups!

Response 5:

Thank you for your suggestion. We have included the power analysis for the non-inferiority objective in the paper.

(lines 305-308) 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.

Comment 6:


Response 5:

Thank you for your suggestion. We have revised the sentence as suggested.

Comment 7:
Line 160 (and in other places): “potential biomarkers and predictors”. Biomarkers are also predictors. Maybe rephrase to “potential biomarkers and other predictors”.

Response 6:

Thank you for your comment. We have revised the sentences as suggested.