Author’s response to reviews

Title: TREATMENT OF SLEEP DISTURBANCES IN TRAUMA-AFFECTED REFUGEES - STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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Author’s response to reviews:

Dear Trials editorial team and reviewers

Thank you for the very useful comments to our paper that we have carefully considered and tried to incorporate into the paper. Our responses to each comment are highlighted in the text below, and changes are made with track changes in the main manuscript attached.

Response to Reviewer

Associate editor:

This is a fine manuscript and important work. In addition to the reviewers comments I have some remarks about the sample size calculation. First, intuitively 32 patients per group does not sound like a lot for an 'add on' intervention. TAU may also decrease sleep problems. Second, if ITT analyses are conducted, treatment drop-out is not a problem and missing data can be imputed (if not too much data is missing). Third, I do not understand the authors rationale to go from the original 128 participants to 228 when they expect a drop out of 25% (I would expect an increase of 32 participants in total). Lastly, I expect that the power will only be sufficient to detect differences between the active treatment groups and the control group and not to detect differences between the three active groups. If so this should be mentioned in the power calculation and/or the discussion.

Response:
This is a very important point. The sample size is calculated based on a hypothesis of add-on mono-treatment being superior to TAU, and add-on combination-treatment being superior to add-on mono-treatment. However, in previous studies of treatment of PTSD in trauma-affected refugees at CTP, only very small effects of treatment were found, hence, it may not be possible to show a clinically relevant difference in symptoms, e.g. 2.5 scale points on PSQI between TAU, add-on mono-treatment and add-on combination-treatment. A larger sample could possibly show a statistically significant difference, for instance 1 scale point between add-on mono-treatment and combination-treatment. However, in this study we have focused on studying changes expected to be of clinical significance.

We have added the following to address the above mentioned issues on drop-out:

“Due to the expected large drop out a formula (k = 1/(100%-dropout%)2) calculating the enhanced number of patients needed in each group was used. We increased the number of patients included with a factor k=1/(100%-25%)2=1.78 x 128 and consequently estimated a total sample size of 228 patients.“

Reviewer #1: Sleep disturbances in individuals suffering from PTSD are one of the key symptoms of this disorder and given the large number of refugees suffering with PTSD more evidence is crucial in decreasing their burden. The manuscript is important and noteworthy. Rationale for conducting the RCT is given in the introduction and the objective is clearly stated. The authors describe with sufficient detail the planned treatments. Nevertheless, the manuscript would benefit if:

Abstract:

1. The discussion part in the Abstract would be more specific. Currently this part starts with: "The trial will contribute with important knowledge in this field" which is a very generic sentence. I would suggest going into detail and stating the important knowledge specifically.

Response:

This has been addressed.
Background:

2. In the Background section the authors state: "Approximately 21.3 million of these people were refugees." Were should be replaced by "became".

Response:

This has been changed.

3. Same section, the authors state: "These numbers are increasing every year" Could you briefly elaborate?

Response:

A sentence has been added to elaborate.

4. Same section, the authors state: "Clinical guidelines for treatment, derived from research on populations with single or few traumatic experiences, fail to account for the specific, prolonged and repeated trauma and post migration stressors experienced by refugees, and cannot be assumed to apply to trauma-affected refugees in general (5,6)." Why not? Please elaborate based on the literature.

Response:

We have added a few sentences to elaborate based on the literature.

Sleep Disturbances:

5. Please mention in the text were the Competence Centre for Transcultural Psychiatry (CTP) is located.

Response:

This has been added.

6. The authors state: "Following treatment of PTSD, sleep disturbances often persist (11,12). Untreated sleep disturbances can contribute to maintenance and exacerbation of both sleep-
related and not sleep-related PTSD symptoms (7,11).” The authors should elaborate what specific type of treatment they mean. Psychotherapeutic treatments, such as CBT or EMDR? Or perhaps Psychopharmacological treatments? Furthermore, how much is often?

Response:

This has been added.

Treatment of sleep disturbances:

7. The authors should state the target groups being addressed in these trials.

Response:

This has been added.

8. The authors state: "Current CBT for PTSD have been found less effective in treating sleep disturbances (12).” Less effective compared to which comparisons?

Response:

The sentence has been edited.

9. The authors state: "A number of treatment manuals exist for both CBT-I and IRT which differ in content complicating comparison and identification of active components of the two treatments" please cite.

Response:

This has been added.

10. The authors state: "In 2015, CTP completed a pilot study on IRT focusing on compliance and acceptability. The pilot study delineated IRT as a fully acceptable treatment for this population, but did not allow for statistical analysis on outcome (29)." How can a treatment be considered fully acceptable if the study couldn't analyse their results?

Response:
The study design only allowed for qualitative analysis and not quantitative statistical analysis. This information has been added in the paper.

11. Is this IRT manual published or available online? If yes please cite.
Response:
This has been added.

Research objectives and hypotheses:
12. Words such as "and, or" do not need to be in italics. Please change
Response:
This has been changed.

Methods:
13. The authors state: "The course of treatment is divided in two phases: phase 1 (initial app. 2 months) and phase 2 (app. 4-6 months)." What does app. mean? Please describe your abbreviations or write in full. Furthermore, after this sentence the following paragraph misses a title such as "outcome measures".
Response:
This has been changed. The following paragraph has been moved and combined with the paragraph Outcome.

14. When the authors mention the secondary outcomes the objective sleep length is not stated anymore although it was in the abstract.
Response:
This has been added.

15. I would suggest moving the blinding and randomization section after the methods for the sake of clarity.
Response:

The order of paragraphs follows the SPIRIT checklist.

Trial fidelity:

16. Are these manuals the authors mention available online? If yes please cite.

Response:

This has been added.

17. The authors mention: "It is also registered whether topics of social character dominated in the session" Could the authors briefly explain the reason for this?

Response:

This has been addressed.

Inclusion criteria:

18. The authors state the following as an inclusion criterion: "Refugees or persons who have been family reunified with a refugee" Please describe this point clearer. Do you mean you are also including family members who didn't became refugees themselves but have been reunified with a family member who became a refugee?

Response:

Often one member of a family flees the home country and becomes a refugee in a host country. If a family member of the refugee becomes family reunified at a later point, they tend to share pre and post migration experiences. Family reunified and refugees alike are only eligible to this trial, if they have experienced traumas and suffer from PTSD.

19. In the exclusion criteria the authors mention "lack of informed consent". Since this criterion has already been mentioned in the inclusion criteria I would not mention it again in the exclusion criteria.

Response:
This has been added on demand from the The Regional Committees on Health Research Ethics for the capital region of Denmark.

20. I would suggest describing the treatment conditions and TAU more concise (3 pages are definitely too much!) and without repeating information that has been mentioned before, such as "CBT is recommended as first-line" or the fact that interpreters are present.

Response: Thank you for pointing this out. The paragraph has been edited. We have chosen to keep the remarks on interpreters since this is an important matter in Transcultural Psychiatry/refugees.

Outcomes:

21. The authors already mentioned briefly after the methods section certains details about the outcomes. I'd suggest combining this parts with this section for the sake of clarity.

Response: The two sections have been combined.

22. The authors describe their outcome measurement tools very detailed. I'd suggest to report them in a more concise way.

Response: The section describing the outcome measures has been revised and superfluous details have been deleted.

23. The authors mention: "The CTP Predictor Index was developed in relation to a previous trial at CTP to register and rate the psychosocial resources of the individual participant." Please cite.

Response: This has been added.
24. The authors stated: "At each consultation with a physician, the participant's condition is assessed through a standardised clinical examination covering 14 parameters." What are these parameters?

Response:

A few examples of the parameters have been added.

25. Please describe briefly the structure of the patient satisfaction survey.

Response:

This has been added.

Randomisation:

26. The authors state: "All participants are randomised after the two-three hour pre-treatment assessment by a physician in accordance with inclusion and exclusion criteria including informed written consent" Since the authors included the informed consent in their inclusion and exclusion criteria there is no need to mention it again separately.

Response:

The paragraph has been edited accordingly.

27. The authors use the term participant and patient interchangeably. I would suggest using the term patient and stick to it.

Response:

Thank you for pointing this out. We have replaced participant with patient.

Discussion:

28. The discussion section is rather short compared to the size of the other sections of the manuscript.

Response:

The discussion section has been expanded.
29. Abbreviations should be described in the text. There is no need for an extra list after the trial status section.

Response:

This is according to the manuscript guidelines of Trials.

Table and figure:

30. I suggest the authors to adapt the current table of collection of data and make it according to APA. This should enhance clarity. Furthermore, abbreviations need to be described under the table.

Response:

The table has been edited according to the SPIRIT guidelines for figures/tables and a list of abbreviations has been added.

31. In the flowchart one of the last boxes below includes certain lines that need to be deleted.

Response:

We are uncertain what this refers to?

All the best

On behalf of the authors

Hinuga Sandahl