Author’s response to reviews

Title: Reducing the frequency and severity of auditory hallucinations: A randomised clinical trial of a novel Audio Visual Assisted Therapy Aid for Refractory auditory hallucinations (AVATAR therapy) compared to supportive counselling

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Author’s response to reviews: see over
Dear Editors,

Thank you very much for your invitation to submit a revised version of our paper for publication in *Trials*.

We were very pleased to read in the feedback that the Reviewers found that “AVATAR is an interesting, innovative and high-tech treatment aimed to decrease auditory hallucinations” and that the manuscript “has importance in the field of psychology and psychiatry”.

The reviewer also raised some important issues that needed to be addressed, and made a number of suggestions for improvement. We are very grateful for these helpful comments and for the opportunity to address these comments and revise our paper.

**Minor essential revisions:**

**Title and abstract**

1. The study seems to include more objectives than the one mentioned in the abstract (clinical effectiveness); the study also contains an economic evaluation, and it will also include qualitative data, mediators and moderators. The authors may wish to include these objectives to the abstract as well.

These objectives have now been included as secondary goals of the study in the abstract section.

2. Please add : ‘Protocol of’ a RCT.. to the title, and add the full institutional addresses and email addresses of all authors to the title page.

The title of the manuscript has been changed in order to fit the journal requirements.

3. Please include the research setting in the method section of the abstract.

This information has been included in the abstract section.

**Introduction**

4. Pilot study: could the authors provide information about the feasibility of the pilot study, and how well the avatar resembled the persecutory voices of the participants?
Further information about the feasibility of the pilot study in terms of acceptance and dropout has been included. We have added a comment on voice matching in the introduction (“Pilot Study” subsection).

5. The study hypotheses d and e (mediators and moderators) have not been embodied in the background. Please describe previous literature on potential mediators and moderators in the introduction section. Furthermore, the cost-effectiveness hypothesis is missing.
The rationale for the study’s exploratory mediators and moderators has been added in the Introduction section.
The cost-effectiveness hypothesis has been added.

6. There are some type-o’s
We’ve conducted a grammar and spelling review of the manuscript.

Methods
7. Which diagnostic interview will be used to assess psychosis, who and how are the assessors trained?
The OPCRIT checklist system will be used to reassess participants’ diagnosis by a trained independent psychiatrist. This information has been added into the manuscript.

8. Please add psychometric properties and assessment method (paper-pencil, online…) to the questionnaires.
The psychometrics of the primary outcome measure (PSYRATS-AH) have been added to the “Measures” subsection. In the interests of brevity and given that most measures are well established, and following other relevant similar publications in this journal (see Freeman et al. 2015 or Waller et al. 2014) we suggest that we do not report these for all secondary measures, although if the editor requests it, we can do so.
All the measures used in the study are been applied in paper-and-pencil format and this is now specified.
9. Which potential mediators/moderators will be included?

We felt that it would be clearest to outline the potential moderators and mediators in the hypotheses, towards the start of the paper, and not repeat in the Statistics section- i.e.

“d) The mediators of treatment effects for AVATAR therapy on changes in auditory hallucinations will be beliefs about voices (specifically omnipotence and malevolence), beliefs about the self (improved self-esteem), appraisal of voice relationship (specifically relative power and assertiveness), and reduction in anxiety.

The moderators of the treatment effects for AVATAR therapy will be number of voices, type of content (derogatory vs. non-derogatory), ratings of the created voice/image, beliefs about problems and social support.

If you prefer the specific moderators and mediators could be repeated in the Statistical analysis section but we were mindful of the word count and avoiding duplication of information.

10. AVATAR therapy: for replication purposes: could the authors provide a reference or a description of the development of AVATAR (e.g. which software has been used, which method is used to develop the avatar and determine the resemblance of the voices, which therapy techniques are being used [cognitive therapy, …], provide examples of the therapeutic interventions. Would be interesting to include the website URL or screenshots of the therapy. What do the authors mean by ‘discussion’ and ‘closely monitored’? Please operationalize.

Some screenshots depicting examples of avatars have been included in the manuscript (Figure 2). For further information about the software, the reader is re-directed to the pilot study publication.

‘Discussion and closely monitored’ has been operationalized:

“The total number of sessions can be extended by up to 3 further sessions where there is a clear rationale for the likely benefit of additional sessions, such as evidence of delayed and ongoing improvements during later sessions, on self-reported severity, content, malevolence or frequency of the voice (any additional sessions are agreed by consensus within the therapy team). Evidence of any adverse reactions will result in completion of an adverse events form (see safety assessment section below).”
11. Therapists of the AVATAR therapy: please include information of the clinical background and training of AVATAR to the manuscript. This information has been included under the subsection “AVATAR therapy”.

12. As Supportive Counselling is meant as a control group, will participants be able to attend AVATAR therapy afterwards?
Yes, they will be included in a waiting list and will be offered AVATAR therapy after the end of the trial ie after all final follow ups. This information has been added at the end of the subsection “Planned Interventions”.

13. Power calculations: might be underpowered for mediators/moderators. Have the authors conducted power calculations for this type of analysis?
We acknowledge this is likely to be case for moderator analysis, since this typically requires up to 4 times as larger sample to detect interaction effects of the same magnitude as the main (treatment) effect. However, it would not be reasonable or feasible to power our trial to detect these effects. Therefore our moderator analysis will be exploratory.

There is no recognised approach for calculating power for causally valid mediation effects. Kenny and Judd (2014) showed that, in many settings, power to detect indirect effects is greater than that for total effects, and power to detect direct effects is less than that for total effects. Therefore we consider that we might be able to perform our mediation analysis with sufficient power to detect indirect effects; however, this depends on the size of the indirect effect in question, and such information is not available a priori.

14. Health economic analysis: the authors are advised to use the CHEERS checklist for economical evaluations which provides guidelines on how to report CEA/CUA (Husereau et al 2013; Consolidated Health Economic Evaluation Reporting Standards (CHEERS): Explanation and Elaboration..Value in Health (16) 231-50).
As suggested, the authors will use the CHEERS checklist to guide the reporting of the cost effectiveness analyses.
15. Analysis: there will be no test of statistical significance between groups on any baseline variable: why not? Even though they will be randomized, differences between groups at baseline may still exist and may bias results.

We have thought carefully about this, discussed the issue with our trial statistician and looked at CONSORT guidance which recommends not performing statistical tests for baseline differences between groups. We acknowledge that there may be baseline differences, because the randomisation principle only holds over repeated samples of the data and in any one observed sample (such as our trial) bias may occur. However, any differences can only result by chance due to the random allocation, and so CONSORT states that the logic behind performing statistical tests is flawed. Therefore we prefer to follow the guidance in CONSORT statement and not perform tests.

16. Analysis: moderator analysis is missing.
This has been added to the statistical analysis section.

17. Please include information on data management and confidentiality (SPIRIT checklist).
This information has been included in the Methods/Design section.

Discretionary revisions:
1. Qualitative evaluation: it would be interesting to assess data on the experience of therapist using AVATAR as well, as they will have to use it in clinical practice as well, and it could provide valuable information to refine the therapy and for implementation purposes.

The authors have considered this recommendation and qualitative interviews will be conducted with the trial therapists. The inclusion of these interviews have been added in the “Qualitative Evaluation” subsection

Editorial requests:
1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?__________: study protocol for a randomized controlled trial.? Please note that the title in the submission system should match that of your manuscript.

The title of the manuscript has been changed in order to fit the journal requirements.
2. Please include the email addresses of all authors on the title page.
All the author’s email addresses can be found in the title page.

3. Please include the date of registration with the trial registration number at the end of the Abstract.
The date of registration has been added at the end of the Abstract section, along with the trial registration number.

4. Please include a statement in your Methods section explaining that you obtained informed consent from each participant.
This information has been included in the Methods/Design section.

5. Please mention each author individually in your Authors' Contributions section. We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.
We have amended the manuscript as suggested.

6. Please include a figure title and legend section after the reference list.
See captions for figures 1 and 2 after the reference list.