Author’s response to reviews

Title: A protocol for a randomised controlled, double-blind feasibility trial investigating the efficacy of fluoxetine treatment in improving memory and learning impairments in patients with mesial temporal lobe epilepsy: Fluoxetine, Learning and Memory in Epilepsy (FLAME trial).

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Author’s response to reviews:

Dear Lawrence Mbuagbaw,

We would like to thank you and the reviewers for their comments on our submitted manuscript. Our responses to the comments and indications of where subsequent edits to the manuscript have been made can be found below. All edits to the manuscript can be identified through tracked changes in the resubmitted document.
Reviewer 1

The investigators describe a trial to determine the feasibility of conducting a double-blind randomised controlled trial of fluoxetine for the treatment of learning and memory impairments in people with temporal lobe epilepsy. It is a well written report with sufficient details on the procedures and measures. I have the following comments;

1) There is a long list of exclusion criteria. A brief explanation of what makes these participants inappropriate for the trial is warranted.

We have now included brief explanations to the list of exclusion criteria (pages 8 & 9, lines 207-233).

2) Reword the fourth reason for withdrawal. Medications may not be allowed in trial, but it doesn't mean they are "contraindicated". Participants can be withdrawn if they a prescribed any medications not allowed in the trial.

We have edited the sentence to read “4) requires prescription of any medication that should not be taken in conjunction with fluoxetine as detailed in prescribing guidelines” (page 14, line 379-380).

The progression criteria are clearly outlined.

3) Discuss any strengths and limitations of the pilot study, if any. I see novelty, the real-world tests and the collection of qualitative data as strengths.

We thank reviewer for their comments. We have already included sections I the discussion on the use of novel and real-world tests and the collection of qualitative data, but we have now highlighted these as particular strengths of the study. We have also added some further material in the discussion section to discuss potential limitations of the study regarding restrictive exclusion criteria and generalisability (page 19).

Reviewer 2

This is a protocol for an interesting feasibility study preceding a clinical trial investigating the efficacy of fluoxetine treatment in improving memory and learning impairments in patients with mesial temporal lobe epilepsy. There is a growing interest in the use of fluoxetine in this field, therefore the trial will address and unmet need. There are a few issues that would be important to improve before moving forward:
1) The most important issue is that along the manuscript, at times it is hard to understand if the authors are talking about the feasibility study or the actual clinical trial they intend to conduct in the future.

We have added text at the end of the introduction section to clarify that this is a feasibility study to be conducted prior to a Phase II efficacy study (also please see response to point 3 for further response). (page 6, lines 146-152)

2) In the introduction part, it would be important to cover in the relevance of the topic, for instance mentioning that TLE is the most common form of epilepsy in adults, its prevalence, a bit of clinical presentation, etc… so that readers become familiar with the condition. This is important given that this is not a neurology/epilepsy journal. The introduction is mostly dedicated to hippocampal neurogenesis. This is a great rationale section for a grant proposal, however, for the protocol article this could be written more objectively, more details could be provided regarding the clinical impact of the problem and need to address it.

We have now included some additional information regarding clinical presentation of TLE and it’s prevalence in the introduction (page 1, line 56-63). We have also emphasised the section on the prevalence of learning and memory problems in people with TLE in the introduction (page 1, line 64-72). However, we have retained the information on hippocampal neurogenesis, it’s relationship to hippocampal sclerosis and its putative role in the learning and memory problems of people with TLE as it provides the rationale for undertaking this study, including the evidence of efficacy from animal studies.

3) In the methods part, it is not very clear that this is a feasibility protocol for a future phase II study. It that what the authors mean? At times it is hard to identify if the authors are talking about the feasibility study or the phase 2 trial they intend to conduct.

We have referred to this trial as being a ‘Phase II feasibility’ trial as the trial meets the categorisation criteria for a phase II trial but is not powered for efficacy. Further the primary objective is centred on feasibility not determining the efficacy of fluoxetine treatment in this context. However, we recognise that the use of ‘Phase II’ terminology in this manner could be confusing and have now removed reference to ‘Phase II’ for clarity (page 6, line 157).

4) The inclusion criteria are very well defined. I just wonder what about patients with TLE without evidence of HS in the MRI? What about people with EEG suggesting TLE from
bilateral source but with unilateral HS? The authors don't say anything about EEG criteria for inclusion.

We have chosen not to include participants with a diagnosis of TLE without confirmation of HS as temporal epileptiform discharges on EEG cannot be definitely localised to mesial temporal lobe structures and may originate in the neocortex of the temporal lobe. This also applies to those participants who may have bi-lateral EEG signs but only uni-lateral HS on MRI. As the rationale for this trial is dependent on potential deficits of neurogenesis within the hippocampus, these participants are not included. We have added a sentence in the section on exclusion/ inclusion criteria to describe this (page 9, lines 235-241).

5) Randomization methods: in the feasibility study, is the ratio fluoxetine: placebo 1:1?

The ratio of randomisation is now included (page 13, line 367).

6) Regarding the healthy controls related to the patients - how do the authors plan to use their data?

In the section on recruitment and consent we have indicated in which assessment data from healthy controls will be used. In the methods section where the procedure for the Sensecam assessment is detailed we had already included a sentence on how the accompanying healthy volunteer would provide ‘control’ comparator would be used. We have now added some further clarity in this section (page 12, lines 320 &321).

7) With respect to secondary outcomes: 4) "investigate if hippocampal microstructure correlates with allocentric learning and memory deficits and/or the response to fluoxetine". Can the authors provide more detailed information on how they aim to investigate this? Is this with 3T MRI? Which MRI sequences are used to define this? Has this been demonstrated before, the tissue microstructure?

The details on how this will be performed is in the section on 3T MRI assessment. We have now made it clearer that the captured images will be used for the investigation of hippocampal microstructure correlates. The novelty of this assessment is highlighted and now included in the discussion as a strength of the study (page 13, line 352-359 and page 19, lines 514-520).

8) Overall assessment: It is important issue to keep in mind is that depressive symptoms frequently cause cognitive problems, and the authors need to clearly define how they will
mitigate the confounding effect of depression in increasing cognitive issues, and responding to fluoxetine when considering efficacy of fluoxetine.

We thank the reviewer for recognising this very important point regarding the design of the trial. Our listed exclusion criteria specifically exclude those participants with active depression or anxiety for this very reason. We have made this rationale more explicit in the section on exclusion criteria and have acknowledged this a limitation of the study in the discussion (page 8, lines 215-219 and page 19, lines 508-513).

9) And also keep in mind that the clinical trial will measure the symptomatic effect of fluoxetine on cognition in this population, as it is not possible to directly measure neurogenesis in this population with the applied MRI technique (or it is? Please provide detailed information on this if possible, or acknowledge the indirectness of this measure).

We agree with the reviewer that any potential changes measured in our chosen outcomes will be symptomatic of fluoxetine treatment. We have made this more explicit in the discussion on p.19 and have acknowledged that the analysis of 3T MR images will not be a direct measure of changes in neurogenesis (page 19 line 517).

Minor issues:

10) Line - 78/79 - neurogenesis in the hippocampus - please provide reference.

This reference is now included (now line 99).

11) Line 102/104 - fluoxetine promotes neurogenesis - provide reference

This reference is now included (now line 117)

12) Lines 234 and 235 - description about pattern separation tasks - should this be moved to introduction and only the methods for the assessment be kept in the methods? Same for line 251.

These sections have now been moved to the introduction (pages 5 & 6, lines 136 – 146).