**Reviewer’s report**

**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)

**Version:** 1  **Date:** 03 May 2019

**Reviewer:** Camila Aquino

**Reviewer's report:**

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 an unmet need. There are a few issues that would be important to improve before moving forward:

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.

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.

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.

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.

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

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

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. 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).

Minor issues:

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

Line 102/104 - fluoxetine promotes neurogenesis - provide reference

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.

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