Reviewer’s report

Title: Effectiveness of Yi-Zhi-An-Shen Granules on cognition and sleep quality in older adults with amnestic mild cognitive impairment: protocol for a randomized, double-blind, placebo-controlled trial

Version: 0 Date: 16 Feb 2019

Reviewer: Ying Zhang

Reviewer’s report:

This is a randomized, double-blind and placebo-controlled trial to evaluate the efficacy and safety of Yizhianshen Granules on cognition and sleep quality. Some methodological issues are still waiting to be resolved.

1. Abstract. Methods/design: the authors mentioned "a placebo-matched group in a 1:1 ratio", will this trial use any matching technique when randomization? If so, authors should state which factor(s) was/were used to match.

2. Design. Para2, L4. The statistician who act as the random coder should be shielded from not only subject recruitment but also statistical analysis.

3. Primary outcome. The hypothesis is confusing. For ADAS-cog11, if the increased score will indicate greater severity, I think the change from baseline to endpoint (baseline-week16) in treatment group will be supposed larger than that in placebo group. If you regard the difference week16 to baseline (week16-baseline) as the outcome, you'd better to specify the formula direction.

4. Sample size. As this trial is a RCT, I don't think the pre and post scores are enough to determine the sample size. It will be better for authors to provide specific parameter alongside the formula used.

In addition, as the comparator in this trial is placebo, why use non-inferiority principle (this design usually used when comparing with an active drug)?

5. Statistical analysis, Para2. It's not wise to state FAS, PPS, and SS in a general way. Instead, especially in a protocol, it's important to state clearly the definition of each in your trial (also consider the particular situations may occur in your trial) one by one. And which kind of analysis will be conducted in each population.

6. Statistical analysis. It said that standardized mean differences will be the effect sizes. Although generally mean differences were more often used, if authors confirm standardized mean differences will be used, it will be better to use it when computing sample size and list references.
7. Statistical analysis. ANOVAs, I don't think you need ANOVAs to compare two groups. Do you mean ANCOVA?

8. Statistical analysis. Para2, last line. The probability of CI for one-sided P value of 0.05 is 90% instead of 95%. If this trial aimed to get 95%CI (the wider one), the one-sided p value should be 0.025 (ie. two-sided p value of 0.05).

9. In the protocol of a double blinded trial, unblinding procedure, both emergency code broken and final unblinding for analysis should be stated in detail.

**Level of interest**
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Quality of figures**
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

**Statistical review**
Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?
4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal

Were you mentored through this peer review?

No