Author’s response to reviews

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

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Author’s response to reviews:

We sincerely appreciate for the reviewer's and the editor's attentions and comments on this study protocol. We have checked and revised the manuscript according to these kind advices and detailed suggestions. We submit here the revised manuscript. Enclosed please find the point-by-point responses to the reviewer and the editor. We sincerely hope this manuscript will be finally acceptable to be published on Trials. Thank you so much for all your help.

If you have any question about this protocol, please don’t hesitate to let we know.

Response to the reviewer’s comments:

Comment 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.
Response: Thanks for the reviewer’s correction. In terms of randomized controlled trial, we are sorry to make a mistake here, and we deleted the word “-matched” in the abstract.

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

Response: We have modified and supplemented some details about randomization making and statistical analysis as follow.

“A statistician expert will act as the coder and be shielded from subject recruitment.” – “The statistician expert who acts as the coder will be shielded from subject recruitment and statistical analysis, which will be performed by another statistician independent of the study group.” (Design. Para2, L4)

“Analysis will be conducted by another statistician of the National Clinical Trial Center of Chinese Medicine (Chengdu, China), who will be blinded to the whole trial …” (Statistic analysis. Para1, L1-2)

Because of these modification, we mentioned another statistician in our acknowledgements.

Comment 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.

Response: These suggestions are really important for us. Then we have made some modifications in the section “Primary outcome” as follow.

“Cognitive decline is measured using the Chinese version of the Alzheimer Disease Assessment Scale-Cognitive subscale (ADAS-cog11). It was also chosen to calculate the sample size, for a 4-point change in it as the measure of clinical significance [42]. The total score is 70. A score increase indicates greater severity of impairment. The specific hypothesis is that the increase from baseline to endpoint will be significantly less at least 2.5 points than that for placebo.”

One reference has been added to the present revision of this protocol as follow.

Comment 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)?

Response: Thanks for the reviewer’s insightful comments. However, as we mentioned before, we quoted the reference to decide the primary outcome. For the limited study period, we didn’t choose the rate of MCI progression to AD, but we expect that the standard of evaluating clinical efficacy recommended in the clinical practice guideline of dementia in China will also be worked in this study. Parameters in the formula used to calculate the sample size involves the values of $\alpha$ and $\beta$, and the allocation ratio of two groups (1:1), in order to avoid repeating narration, we didn’t clarify the specific formula here. The formula is as follow.

$$n_1 = \left[ \frac{(u_{1-T} + u_{1-U})e}{W} \right]^2 + \frac{(1+c)}{c}, n_2 = cn_1$$

In this formula, $U_{1-T} = U_{1-\alpha} = 1.64$, $U_{1-U} = U_{1-\beta} = 1.28$, $c = 1$, the values of $e$ and $W$ are based on the previous clinical trial we quoted.

Because there is no effective treatment strongly recommended in existing clinical practice guidelines of MCI, we chose placebo as the controlled treatment in this study. Meanwhile, we expected that the efficacy of this herbal formula could be superior to or at least equivalent to the placebo and used non-inferiority principle, since there exist placebo effects.

Comment 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.

Response: We really appreciated the helpful advice. And we have modified the expression in the “Statistical analysis” section.

Comment 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.

Response: Thanks a lot for the correction. As for effect size, we have changed the expression “standardized mean differences” to “mean differences”.

Comment 7. Statistical analysis. ANOVAs, I don't think you need ANOVAs to compare two groups. Do you mean ANCOVA?
Response: The consideration of the reviewer’s is really insightful. We thought before that when it comes to the statistical differences between two groups, if the quantitative data conform to the normal distribution, both Student’s t test and one-way AONVA can get the same results. But now, we have corrected our mistake in the “Statistical analysis” section.

Comment 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).

Response: We are sincerely grateful for the correction, and we have corrected the expression and our subsequent statistical analysis.

Comment 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.

Response: We have added these statements in this revised protocol in “Quality control and monitoring” section, Para2-3.

Responses to the editor's comments:

Comment 1. The protocol should be consistent across document in terms of primary, secondary, and exploratory objectives and corresponding outcome measures. In particular, the objectives stated that as primary objective, efficacy and safety will be assessed, while only an efficacy measure (cognition) is stated under measures, and safety measures are listed only as “other” measures.

Response: We have amended the subtitle “Other measures” to “Safety outcomes”, and supplemented the time to get these safety indicators. We also deleted the words “and safety” in “Methods, Objectives (Para1, Line1)”.

Comment 2. The protocol should be more detailed regarding the assessment of safety and tolerability (which is actually not mentioned). Stated as primary objective, the background should elaborate more on safety data of the experimental treatment (from human or non-human data), including what would be potential / expected AEs the investigator would need to screen for. In particular, the outcome measure section mentions MRIs and ECGs, as well as vital signs and weight as safety outcome measures, but it is not clear when and at what frequency these will be obtained.

Response: Thanks for the editor's consideration for the safety and tolerability assessment. In order to make a clear expression, we have added relevant statements about safety measures in both “Statistical analysis” and “Quality control and monitoring”. There is an illustration in the Fig.1 Schedule of interventions and assessments.
As for the assessment of tolerability, Yi-Zhi-An-Shen Formula is an empirical herbal formula coming from clinical practice of Chinese medicine, the clinical practitioners have found the suitable dosage range of each herb involved in this formula. Besides, the research team has performed pharmaceutical experiments and animal experiments on tolerability and pharmacology. These experiments are mentioned in this protocol, and reference No.37 and No.38 are also quoted, though they are published in simplified Chinese. That’s the reason why we did not include the tolerability assessment in this clinical study.

Comment 3. The protocol lacks a detailed SPIRIT diagram. The current table is insufficient, as it only lists a selection of the measures listed in the manuscript. In particular, the diagram should be complete in terms of safety measures

Response: Thanks for the suggestion. Thus, we added the expression about safety outcomes in the description of Item No.12 in this SPIRIT diagram, and renewed the corresponding page numbers.

Comment 4. DNA analysis is listed as exploratory outcome, including an effort to genotype fecal DNA. Although exploratory, the authors should give some insight into how this particular dataset would be analyzed, as depending on the markers assessed and the estimated effect sized, this study is likely highly underpowered to draw any inferences.

Response: We have added some narration to our statistical analyses about gut microbiome (Page 15-16).

Comment 5. As this study will be conducted at multiple sites, please specify whether the IRB approval covers all study-sites.

Response: Thanks for the recommendation. We added this statement in the “Design” section in this revised protocol.

Comment 6. Exclusion criteria #3: please clarify which disease modifying treatments you are referring to, or whether this exclusion criteria refers to subjects participating in clinical trials on potentially disease modifying interventions

Response: We have made a supplementary clarification in brackets at the end of the third criterion.

As for the additional comments by the Editorial Office, we feel really grateful for these thorough explanations and recommendations. During the recruitment and consent process, we always try our best to keep the caregivers or eligible informants (the individuals who stay with the participant for at least 20 hours per week, sleeping hours are not counted) accompanying the
participants. But we didn't mention that in the previous manuscript. And then we added this statement in the "Design" section in this revised protocol.