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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Reviewer 1#:

Q1.

As it mentioned in the feedback, doesn't it mean that the design ought to be "superior" instead of "non-inferior"? In addition, either "non-inferior" or "superior" needs a cutoff, meaning minimal clinically important difference (MCID), to declare how larger effect size of the herbal than placebo could be regarded as large enough from the clinical perspective when choosing superior design, or how smaller is thought as acceptable when using non-inferior design.

A: We're sincerely appreciate your helpful recommendation. We just ignored the significance of effect size when we conceived this protocol in the beginning. We suppose it's not too late to modify this flaw. But we have added this content in the section 4.1 sample size in our new revised version, and we still referred to some data from one published trial with similar design, which was quoted as the reference No. 43 in our manuscript. Adding this effect size did not
change greatly the minimal number of participants in the treatment we need, so we still calculated an approximate value of 33 and held the total number of 80.

As for using non-inferior design, we have consulted literature with the same goals or similar therapies on mild cognitive impairments. Exceptionally, we did see some clinical studies demonstrating placebos have some effects of delaying cognitive decline on MCI, especially in some blinded ones. As one mental dysfunction, maybe the placebo does play a role in psychological hint and treating this disorder. Moreover, even in the latest clinical practice guideline of cognitive impairment and dementia of China, there still lacks etiological medication for MCI due to neurodegeneration. Thus, we supposed that the placebo effect should not be neglected until certain etiological drugs are discovered, and we drafted this protocol with non-inferior design.

Since there're really exist some difficulties in recruiting enough qualified older adults with aMCI, we didn't plan a blank control group in this study. However, we are endeavoring to collaborate with another community hospital to take part in the study. If we make it, we will make modifications on the ClinicalTrials.gov soon.

Editor’s comment:

There is one additional outstanding item: the comment regarding the SPIRIT diagram was directed at the figure / schedule of assessments. Please update this schedule of assessment figure to be comprehensive containing all assessments / for efficacy as well as safety outcome.

A: We're really sorry about our misunderstanding of this comment before and then we just didn't make any change in the first revision. Here, we sincerely apologize for this ignorance, again.

According to the SPIRIT-Figure, We have renewed the figure of the schedule, and added the corresponding outcomes we will conduct, also added some explanations in the abbreviation section at the end of this modified manuscript.