Author's response to reviews

Title: Exploring Effective Core Drug Patterns in Primary Insomnia Treatment with Chinese Herbal Medicine: Study Protocol for a Randomized Controlled Trial

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Author's response to reviews: see over
Dear editor and Prof. John Norrie:

Thanks you very much for your comments and suggestions. We have carefully checked and revised the manuscript and responded, point by point to, the comments as listed below. Since the paper has been revised significantly throughout the text, we only highlight the major amendments in the revised manuscript.

Looking forward to hearing from you soon.

With kindest regards,

Yours Sincerely

Shiyan Yan

**Replies to Reviewers**

The authors need to attend to the following issues to clarify their protocol:

1. The English writing needs checking throughout -there are various mistakes and in several places the protocol lacks fluency.

   **Answer:** the English writing has been carefully checked and revised throughout.

2. The design needs to be more carefully explained and justified -for example:

   a. It seems that all eligible patients are seen by the 3 TCM clinicians, including the 50% that will be randomised to placebo -but that it is only those randomised to TCM that are subsequently seen after randomisation by the 3 clinicians -so (a) how then is this a 'blinded' (b) what is the point of the baseline TCM assessments in the placebo group? They do not appear to be used after they have been taken?

   **Answer:** I am very sorry for my unclear description of the protocol design. The correct design is: Three Chinese clinicians will diagnose and treat every eligible patient individually. Every Chinese clinician will provide CM Patterns and the prescription according to every patient’s disease condition. So there are three prescriptions from
three Chinese clinicians for every patient at every visit. At the first visit, patient will equally be randomized to one of the following four groups: medical group A, B, C or placebo group. Patients in CM group will be given one of three Chinese clinicians’ prescriptions. Patients in placebo group will be given the placebo simulating the core drug patterns in previous study. In the whole study, the randomization of group assignment only conducts at the first visit, and its randomization results will be applied to the following visits. In another words, though the patients have to be diagnosed by every clinician for every visit, they always receive the drug prescribed by the clinician who is distributed to them by randomization at the first visit or receive placebo.

b. What is the overarching purpose of the trial -the title suggests that this is ‘finding the effective core drug patterns’- so is the comparison between placebo and active purely to identify the subset of patients that have responded to then conduct the 'scale free network' analysis o find these core drug patterns? 
Answer: Yes.

c. The protocol states 'At next visits the assignment of group still adopts the randomisation results of the first visit' -so useful to be clear -the patient remains being treated with whatever the initial clinician allocated recommends, but this prescription could be changed and adapt from visit to visit?
Answer: Yes. During the whole treatment, Chinese clinicians can make necessary adjustment in their medicinal prescription depending on the condition of disease.

d. But if so doesn’t that make the prescriptions from the other two TCM clinicians very artificial -because they haven't been treated according to what they recommended? And in a similar vein even though one of them had their treatment implemented, they don't actually know that for sure due to blinding?
Answer: Yes.

3. There does not seem to be any justification of the sample size -we are told it is a sequential design with looks at 80 and 160, and that the maximum sample size will be 300 -but this is not justified in terms of power to detect an assumed effect size nor what variability is being assumed in the Total Sleep Time (TST) primary outcome?
Answer: The study is supposed to explore the daily clinical practice of three prestigious Chinese clinicians in primary insomnia treatment and to figure out the effective drug patterns prescribed by them. However, it is very difficult to estimate the sample size because of lack of previous relevant study. In the previous study, we didn’t obtain the information of TST.

4. But given the objective is to find the 'core effective drug patterns', this isn't driven so much by the 150 patients, but the 3 TCM clinicians. Three seems a very small number, and in addition all three are described as 'prestigious' and 'expert'. So it would seem (a) we are unlikely to find all the core drug patterns due to a very small number of clinicians taking part, and (b) even then the findings may not be generalisable?

Answer: In Chinese medical treatment, different Chinese clinicians possess different ideas on diagnosis and treatment. Therefore, it is possible that one or more than one core prescriptions could be obtained. In this case, the question is raised about whether the explored core prescription can generalized from this relatively small group. On one side, the three Chinese clinicians are experts in this field and can represent the best ones in China. As a result, their prescriptions could be treated as valuable. On the other side, in the study the clinicians are actually considered as treatment instead of sample. Hence, there shouldn’t be a problem with small size for clinicians. Nevertheless, further RCT study will be done to examine the efficacy of the core prescription.

5. We need proper detail and methodological references for the 'multi dimensions association rule and scale free networks method' -and in addition why is this analysis only on those that the treatments proved effective on? And what is the definition of effective for TST?

Answer: The references have been added in the manuscript.

The exploration analysis on core drug patterns will only be based on the effective patients in order to guarantee the efficacy of the explored core prescription. The efficacy can be confirmed only when improvement in TST is bigger than half hour and considered as statistically significant.

6. What pharmacologic insomnia treatments will be allowed and how will this be adjusted for in the analysis, if appropriate?
Answer: Normally, the participants are not allowed to take any pharmacologic medicine used to treat insomnia. However, they are allowed to do so if they could not bear the bitterness brought about by insomnia. Under such circumstances, the dosage and the name of the medicine must be recorded carefully in sleep diaries. And the efficacy for these patients will be assessed using the method ‘Last Observation Carried Forward’.

7. What is the justification for having an upper age limit of 65 years old?

Answer: In order to guarantee the quality of the study, those patients with hypertension, diabetes, stroke and coronary heart diseases are excluded from the study because these patients may demonstrate mixed symptoms or syndromes in the diagnosis that affect accuracy of prescription by clinicians. The patients older than 65 are easily complicated with the diseases mentioned above and then excluded from the study.

8. In addition, the authors should discuss the inclusion / exclusion criteria to explain how generalisable the findings might be? Presumably this is a single site study, as well?

   Answer: Thank you very much for the suggestion. I have added in the revised manuscript.

9. Is the primary outcome of TST by patient self report from a diary validated for use like this in a clinical trial?

   Answer: TST from a sleep diary by patient self-reported has been efficiently used in most of the treatment studies on insomnia. Although it is subjective and there is often a divergence compared with objective (polysomnographic or actigraphy) sleep measures, we think it is accepted as our study is an exploratory study and in clinical practice patients with insomnia don’t receive overnight sleep monitoring.

10. The safety section is very brief and should be expanded. Is there any independent oversight of the trial via a Trial Steering Committee and an independent Data Monitoring Committee?

   Answer: Thank you very much for the suggestion. I have added the description in the revised manuscript.
In order to minimize potential bias and to keep the blind condition of study as possible as one can, all researchers participating in the study are divided into three groups: clinical study group, diagnosis and assessment group, and quality control and statistical analysis group. In the quality control group, there are two persons (the corresponding authors) are responsible for the management and early stopping of the trial. The two persons’ role is similar to the Trial Steering Committee and Data Monitoring Committee.