PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Efficacy and safety of Suanzaoren decoction for chronic insomnia disorder in adults: study protocol for randomized, double-blind, double-dummy, placebo-controlled trial</th>
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<tr>
<td>AUTHORS</td>
<td>Zhou, Qi-hui; Wang, Hui-lin; Zhou, Xiao-li; Xu, Meng-bei; Zhang, Feng; Huang, Bo; Zheng, Guo-qing; Lin, Yan</td>
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VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Cun-Zhi Liu</th>
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<td></td>
<td>Acupuncture and Moxibustion Department, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University.</td>
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<td>REVIEW RETURNED</td>
<td>03-Oct-2016</td>
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GENERAL COMMENTS

This is a very interesting and well-designed study protocol entitled “Efficacy and safety of Suanzaoren decoction, a classical herbal prescription, for chronic insomnia disorder in adults: study protocol for randomized, double-blind, double-dummy, placebo-controlled trial” by Zhou et al. Therefore, my comments are minor as follows. Major Compulsory Revisions
1. Secondary outcomes, "the sleep diary is conducted daily from one week at baseline to the last follow-up” What is the purpose to ask the subject to keep record everyday? What is the plan to analyze those data?
2. For the feasibility of this study, please specify the concomitants and forbidden drugs.
3. The authors should introduce the methods of Statistical analysis.
4. The information of preclinical trials is important for scientific judgement of this study. Please add it on.
5. Routine laboratory tests, such as blood cell analysis and liver function, should be considered during the period of screening and the end of study, in order to ensure the safety of the subjects.

Minor Essential Revisions
1. The educational background of the researcher and the training for the diagnostic interview should be provided. Who make the diagnosis of insomnia disorder?
2. The authors should explain the date of the study started and ended, add the date of registration of Trial Registration.
3. Please indicate the follow-up period in the Flow diagram.
4. Inclusion and exclusion criterias, please pay attention to tense.
5. The authors should introduce why Zolpidem tartrate was chosen as control group. SZRD granule was used in this study. What’s the difference between granule and decoction? The authors should introduce the ingredient of the SZRD granule placebo and ZT placebo.
6. Ethics and dissemination, line 40, change “the” to “The”.


<table>
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<th>REVIEWER</th>
<th>Johannah Shergis</th>
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<tr>
<td>RMIT University; Australia</td>
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<td>REVIEW RETURNED</td>
<td>20-Oct-2016</td>
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</table>

**GENERAL COMMENTS**

This is an interesting and worthwhile study however you have not described the methods in enough details to inform the reader or reproduce the study. Specifically;

1. Consider additional limitations such as un-standardised herbal ingredients. Limited generalisability because this study is only evaluated in the Chinese population.
2. References 10-13 and 19 are not appropriate and you need to find a better reference.
3. You use the past-tense often eg. "The trial was...". This is a protocol therefore you should discuss in the future tense.
4. You have not provided enough information on the statistical analysis. Will you use intention to treat? What method will you use for imputation and why?
5. Use use the term "chronic insomnia disorder" but this phrase is not used in DSM-5 it is used in ICSD-3. It is confusing for the reader
6. Inclusion criteria will have 2 clinicians diagnosing insomnia, what if they disagree how will it be resolved?
7. Will you exclude people taking other herbal medicine?
8. Intervention: Why are patient visits required as frequently as once a week?
9. You have not provided enough detail about the intervention eg. manufacturer, dose with justification. Please follow the CONSORT Extension for Herbal Interventions closely to address all the necessary details about the intervention.
10. What is the placebo made from?
11. Why did you choose zolpidem control?
12. Use plan to assess PSG one night before and after treatment but you note that insomnia is defined as a minimum of 3 nights per week. How do you know the PSG will be conducted on an insomnia night? One night is not enough. You could consider actigraphy with sleep diary verification. In addition, PSG may be more useful for diagnosis for for assessing treatment effect.
13. PSQI includes a question "use of sleeping medication" therefore your results will be difficult to interpret because all people in the zolpidem will score 3 points higher than herbal medicine and placebo group. How will you deal with this issue? Consider removing the question.
14. What does blood, urine and stool routine mean?
15. Why will you withdraw people with adverse events? Your results may appear distorted. You should consider remaining people in the study and only remove if it is unsafe for them to continue. Even so, you should still follow up with them.
16. What about known adverse events of zolpidem. How will you deal with this?
17. How will you measure if subjects do not respond to CBT-I? Who will do this assessment?
18. Acknowledgements: You thank the participants but this is protocol so there should not be any participants yet?
19. Table 1: Change "English name" to "Common name". Family column is incorrect for example suan zao ren Family name is Rhamnaceae. English name of Fu ling is not Indian bread do you mean Indian buead?. You need to use an authoritative reference for this table!
20. Figure 1: Enrollment should be changed to Screening. Also add CBT-I in the flow diagram. Include anticipated number of participants.
Reviewer: 1
Reviewer Name: Cun-Zhi Liu
Institution and Country: Acupuncture and Moxibustion Department, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University.

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is a very interesting and well-designed study protocol entitled “Efficacy and safety of Suanzaoren decoction, a classical herbal prescription, for chronic insomnia disorder in adults: study protocol for randomized, double-blind, double-dummy, placebo-controlled trial” by Zhou et al. Therefore, my comments are minor as follows.

Major Compulsory Revisions
1. Secondary outcomes, “the sleep diary is conducted daily from one week at baseline to the last follow-up”. What is the purpose to ask the subject to keep record everyday? What is the plan to analyze those data?

Re: Thank you for your kind suggestion. The use of a sleep diary is indeed considered as a “first-level” mandatory tool to assess sleep habits and sleep disorders [Natale V, Léger D, Bayon V, Erbacci A, Tonetti L, Fabbri M, Martoni M. The consensus sleep diary: quantitative criteria for primary insomnia diagnosis. Psychosom Med. 2015 May;77(4):413-8.]. Researchers agree that having insomnia sufferers prospectively self-monitor or record their sleep on a night-by-night basis with a sleep diary is a useful methodology for assessment and for tracking treatment effects [Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, Morin CM. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012 Feb 1;35(2):287-302.; Natale V, Léger D, Bayon V, Erbacci A, Tonetti L, Fabbri M, Martoni M. The consensus sleep diary: quantitative criteria for primary insomnia diagnosis. Psychosom Med. 2015 May;77(4):413-8.]. Thus, we ask the subjects to keep record everyday. The sleep diary is designed to gather information about patients’ sleep pattern based on the Core Consensus Sleep Diary [Natale V, Léger D, Bayon V, Erbacci A, Tonetti L, Fabbri M, Martoni M. The consensus sleep diary: quantitative criteria for primary insomnia diagnosis. Psychosom Med. 2015 May;77(4):413-8.] as follows: (1) the bedtime; (2) the time when the patients try to sleep; (3) sleep onset latency; (4) number of awakenings; (5) duration of total awakenings; (6) the time of final awakening; (7) final rise time; (8) sleep quality (rated via Likert scale); (9) open-ended comments from the patients. Total sleep time and sleep efficiency (total sleep time/time in bed*100) are the primary outcome measures that are analyzed, and simultaneously other items above are also analyzed.

2. For the feasibility of this study, please specify the concomitants and forbidden drugs.

Re: We have added as follows:
It is forbidden to combine with other sleep medications in the study. Acupuncture therapy, psychotherapy and any drugs and diet such as psychopharmacological drugs, opioids, anxiolytics, coffee and alcohol that may induce sedative or hypnotic effects are also not allowed in this trial. It is acceptable if patients had already taken medicine that did not act upon the central nervous system before the trial. Yet, all combined administration should be recorded in case report form (CRF).

3. The authors should introduce the methods of Statistical analysis.

Re: We have added as follows:
Data analysis will be performed by professional statisticians using the SPSS software. An intent-to-analysis (ITT) will be conducted for the patients who have received treatment at least once. We will
perform sensitivity analysis by using various imputation methods to detect if the results were robust for different assumptions about the missing data. The per-protocol analysis will be restricted to patients who do not violate the protocol and complete the program. We use Mean±SD for continuous variables and percentages for categorical variables. Analysis of variance is performed on categorical variables and Pearson’s chi-square test on continuous variables. The study will set alpha level of 0.05 two sided for all statistical tests. 95% CI will be used regarding continuous variables.

4. The information of preclinical trials is important for scientific judgement of this study. Please add it on.
Re: We have added as follows:
5. Routine laboratory tests, such as blood cell analysis and liver function, should be considered during the period of screening and the end of study, in order to ensure the safety of the subjects.
Re: We have added as follows:
The safety will be assessed by routine blood test, renal function test, liver function test, routine urine test, routine stool test and electrocardiogram. These indicators are detected during the period of screening and after 5 weeks treatment.

Minor Essential Revisions
1. The educational background of the researcher and the training for the diagnostic interview should be provided. Who make the diagnosis of insomnia disorder?
Re: We have added as follows:
All researchers are the certificated clinical doctors in neurology for at least 3 years, receive a standardized training for the diagnostic interview before trial beginning. Two clinicians make the diagnosis of chronic insomnia disorder.
2. The authors should explain the date of the study started and ended, add the date of registration of Trial Registration.
Re: We have added the dates of the study started and ended. The trial has been registered with at Chinese Clinical Trial Registry (ChiCTR-IOR-16009198) on 13 September 2016 and will be executed from January 2017 to December 2017.
3. Please indicate the follow-up period in the Flow diagram.
Re: We have added the follow-up period in the Flow diagram accordingly.
4. Inclusion and exclusion criterias, please pay attention to tense.
Re: We have corrected the tense in the inclusion criteria and exclusion criteria.
5. The authors should introduce why Zolpidem tartrate was chosen as control group. SZRD granule was used in this study. What’s the difference between granule and decoction? The authors should introduce the ingredient of the SZRD granule placebo and ZT placebo.
Re: Zolpidem tartrate, an imidazopyridine agent, is a widely prescribed medication approved by the

SZRD granule are composed of five Chinese herbal medicines (Spine date seed, Liquorice root, Common anemarrhena rhizome, Indian buead and Sichuan lovage rhizome). Granule is more convenient than decoction for patients in the trail, and patient compliance may be increased. The SZRD granule placebo is composed by 98% maltodextrin, 2% caramel and very little bitterant. ZT placebo is made of starch.

6. Ethics and dissemination, line 40, change “the” to “The”.

Re: We have changed accordingly.

Reviewer: 2
Reviewer Name: Johannah Shergis
Institution and Country: RMIT University; Australia
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
This is an interesting and worthwhile study however you have not described the methods in enough details to inform the reader or reproduce the study. Specifically;
1. Consider additional limitations such as un-standardised herbal ingredients. Limited generalisability because this study is only evaluated in the Chinese population.
Re: Thank you for your kind suggestion. We have added the limitation as follows: Additionally, the study may limit the generalisability since the other populations are not evaluated.
2. References 10-13 and 19 are not appropriate and you need to find a better reference.
Re: We have revised as follows:
3. You use the past-tense often eg. "The trial was...". This is a protocol therefore you should discuss in the future tense.
Re: We have revised accordingly.
4. You have not provided enough information on the statistical analysis. Will you use intention to treat? What method will you use for imputation and why?
Re: We have added as follows:
Data analysis will be performed by professional statisticians using the SPSS software. An intent-to-analysis (ITT) will be conducted for the patients who have received treatment at least once. We will...
perform sensitivity analysis by using various imputation methods to detect if the results were robust for different assumptions about the missing data. The per-protocol analysis will be restricted to patients who do not violate the protocol and complete the program. We use Mean±SD for continuous variables and percentages for categorical variables. Analysis of variance is performed on categorical variables and Pearson’s chi-square test on continuous variables. The study will set alpha level of 0.05 two sided for all statistical tests. 95% CI will be used regarding continuous variables. Missing data will be replaced according to the principle of the last observation carried forward.
5. Use the term “chronic insomnia disorder” but this phrase is not used in DSM-5 it is used in ICSD-3. It is confusing for the reader
Re: The term of “chronic insomnia disorder” is used in ICSD-3. We have revised the sentence accordingly.
6. Inclusion criteria will have 2 clinicians diagnosing insomnia, what if they disagree how will it be resolved?
Re: We resolve it by discussion between the two clinicians or consult with the trail designers (Prof. LiN or Prof. ZHENG).
7. Will you exclude people taking other herbal medicine?
Re: We exclude people taking other herbal medicine.
8. Intervention: Why are patient visits required as frequently as once a week?
Re: A weekly patient visit can increase patient compliance. Through the remaining in the medicine bottle, clinicians are able to estimate weather the patients take drugs according to the instructions. Thus, it is reasonable that patient visits are required as frequent as once a week during the 5 weeks treatment.
9. You have not provided enough detail about the intervention eg. manufacturer, dose with justification. Please follow the CONSORT Extension for Herbal Interventions closely to address all the necessary details about the intervention.
Re: We have added as follows:
ZT tablet is provided by Senofi (Hangzhou) Pharmaceutical Co., Ltd and the dosage strength is 10mg. SZRD granule and its placebo are produced by China Resources Sanjiu Medical & Pharmaceutical Co., Ltd and can be preserved for 2 years.
10. What is the placebo made from?
Re: The SZRD granule placebo is composed by 98% maltodextrin, 2% caramel and very little bitterant. ZT placebo is made of starch. The SZRD granule placebo and ZT placebo are similar to the SZRD granule and ZT in the aspects of size, color, shape, taste, smell and package, respectively.
11. Why did you choose zolpidem control?
12. Use plan to assess PSG one night before and after treatment but you note that insomnia is defined as a minimum of 3 nights per week. How do you know the PSG will be conducted on an insomnia night? One night is not enough. You could consider actigraphy with sleep diary verification. In addition, PSG may be more useful for diagnosis for for assessing treatment effect.
Re: Polysomnography is considered as objectively measuring sleep [Lorenzo JL, Barbanoj MJ].
Variability of sleep parameters across multiple laboratory sessions in healthy young subjects: the "very first night effect". Psychophysiology. 2002;39:409-13. Actigraphy has a high specificity for detecting whether the patient is asleep or awake but cannot differentiate between sleep stages and score REM sleep. Additionally, we have registered in the trail which used PSG as a primary outcome measurement. We will consider actigraphy as a complementary measurement to assess the sleep quality.

13. PSQI includes a question "use of sleeping medication" therefore your results will be difficult to interpret because all people in the zolpidem will score 3 points higher than herbal medicine and placebo group. How will you deal with this issue? Consider removing the question.
Re: We have removed the question accordingly.
14. What does blood, urine and stool routine mean?
Re: The actual meaning is the routine blood test, routine urine test, and routine stool test. We have revised accordingly.
15. Why will you withdraw people with adverse events? Your results may appear distorted. You should consider remaining people in the study and only remove if it is unsafe for them to continue. Even so, you should still follow up with them.
Re: We have revised in safety assessment part as follows: We will withdraw the patients who have severe adverse events as it is unsafe for them to continue the trail. Meanwhile, we will give them relevant medical care and follow them until the reaction has terminated.
16. What about known adverse events of zolpidem. How will you deal with this?
Re: Common side effects caused by zolpidem are tender and light, such as parasomnias, amnesia, hallucinations and gastrointestinal reaction. Generally, it will disappear over time, so strict observation will be given for the patients. Severe adverse events are rare. If it happened, appropriate treatments will be given in time, and we follow them until the reaction has terminated. [Ben-Hamou M, Marshall NS, Grunstein RR, Saini B, Fois RA. Spontaneous adverse event reports associated with zolpidem in Australia 2001-2008. J Sleep Res. 2011 Dec;20(4):559-68]
17. How will you measure if subjects do not respond to CBT-I? Who will do this assessment?
Re: The trail include patient who is unsuccessful to CBT-I alone and has willing to add pharmacological therapy. The CBT-I will be assessed by trail designers (Prof. LIN or Prof. ZHENG).
18. Acknowledgements: You thank the participants but this is protocol so there should not be any participants yet?
Re: We have deleted it accordingly.
19. Table 1: Change "English name" to "Common name". Family column is incorrect for example suan zao ren Family name is Rhamnaceae. English name of Fu ling is not Indian bread do you mean Indian buead?. You need to use an authoritative reference for this table!
Re: Based on the website http://www.theplantlist.org/, we have revised as follows: We have changed “English name” to “Common name”.
We have changed “Family” to “Species”.
English name of Fuling is Indian buead.
20. Figure 1: Enrollment should be changed to Screening. Also add CBT-I in the flow diagram. Include anticipated number of participants in each group. Change "accessed" to "Assessed"
Re: The trail include patient who is unsuccessful to CBT-I alone and has willing to add pharmacological therapy. We have change "accessed" to "Assessed" in the Figure 1.
In addition, the paper needs editing and proofing for English proficiency.
RE: We have carefully checked the entire manuscript again for type mistakes, grammatical errors and misleading statements, and the corrections are highlighted in red in the revised manuscript.
### VERSION 2 – REVIEW

| REVIEWER | Liu Cun-Zhi  
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<td></td>
<td>Acupuncture and Moxibustion Department, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University</td>
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<td>REVIEW RETURNED</td>
<td>31-Dec-2016</td>
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#### GENERAL COMMENTS

The design of the study is very well worked out and objective entitled “Efficacy and safety of Suanzaoren decoction for chronic insomnia disorder in adults: study protocol for randomized, double-blind, double-dummy, placebo-controlled trial” by Zhou et al. Authors made a careful revision of the proposal. However, there are some minor comments as follows:

1. Randomization and allocation concealment author said that “Clinicians who screen the eligible patients will open the envelopes according to the patients' screening sequence numbers, and then assign the patients to treatment group, control group or placebo group in accordance with the group number inside.” It seems that the clinicians who screen the eligible patients know the treatment assignments.

2. Blinding author described that “This is a triple-blind (with patients, clinicians and statistics blinded) trial.”, however, in the title, author introduced that this is a double blind trial, please unify.

3. Data analyses please change “intent-to-analysis” to “intent-to-treat analysis”.

| REVIEWER | Johannah Shergis  
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<td>REVIEW RETURNED</td>
<td>15-Dec-2016</td>
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#### GENERAL COMMENTS

The queries have been adequately addressed. This manuscript is suitable for publication.

### VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Liu Cun-Zhi
Institution and Country: Acupuncture and Moxibustion Department, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The design of the study is very well worked out and objective entitled “Efficacy and safety of Suanzaoren decoction for chronic insomnia disorder in adults: study protocol for randomized, double-blind, double-dummy, placebo-controlled trial” by Zhou et al. Authors made a careful revision of the proposal. However, there are some minor comments as follows:

- Randomization and allocation concealment author said that “Clinicians who screen the eligible patients will open the envelopes according to the patients' screening sequence numbers, and then assign the patients to treatment group, control group or placebo group in accordance with the group number inside.” It seems that the clinicians who screen the eligible patients know the treatment assignments.

Re: Thank you for your kind suggestions. We have revised as follows:

Clinicians who screen the eligible patients will open the envelopes according to the patients’ screening sequence numbers, and then assign the patients to group A, B or C in accordance with the
group number inside.

- Blinding author described that “This is a triple-blind (with patients, clinicians and statistics blinded) trial.”. however, in the title, author introduced that this is a double blind trial, please unify.

Re: We have revised as follows: This is a double-blind (with patients and clinicians blinded) trial.”

- Data analyses please change “intent-to-analysis” to “intent-to-treat analysis”.

Re: We have revised accordingly.

Reviewer: 2
Reviewer Name: Johannah Shergis
Institution and Country: RMIT University; Australia
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
The queries have been adequately addressed. This manuscript is suitable for publication.
Re: Thank you for your positive suggestions.

VERSION 3 – REVIEW

| REVIEWER                        | Liu Cun-Zhi                                      |
|                                | Acupuncture and Moxibustion Department, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University. |
| REVIEW RETURNED                | 26-Jan-2017                                      |

| GENERAL COMMENTS               | This is an interesting study and generally well described in the manuscript. The study design will adequately test the hypothesis, and sufficient details are provided to allow replication of the work. I am agreed that the writing is acceptable. |

| REVIEWER                        | Johannah Shergis                                      |
|                                | RMIT University                                       |
| REVIEW RETURNED                | 09-Jan-2017                                      |

| GENERAL COMMENTS               | No further comments                                      |
Efficacy and safety of suanzaoren decoction for chronic insomnia disorder in adults: study protocol for randomised, double-blind, double-dummy, placebo-controlled trial

Qi-Hui Zhou, Hui-Lin Wang, Xiao-Li Zhou, Meng-Bei Xu, Hong-feng Zhang, Li-bo Huang, Guo-qing Zheng and Yan Lin

*BMJ Open* 2017 7:
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