PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Traditional Chinese medicine injections for heart failure: a protocol for systematic review and network meta-analysis of randomized controlled trials
AUTHORS	Lin, Shan-Shan; Shi, Qingyang; Yang, Fengwen; Wang, Xianliang; Mao, Jingyuan

VERSION 1 – REVIEW

REVIEWER	Lutz Frankenstein University Hospital Heidelberg
REVIEW RETURNED	11-Feb-2020

GENERAL COMMENTS	Thank you for letting me review this NMA-protocol. I have the following comments: * type of participants: a) why restrict to pure CHF? b) how do you define "serious complications or other organic disease"? c) given the co-morbidity burden of CHF, wouldn't that severly truncate your population? * type of intervention: a) though you state "no restrictions to race" you still mandate inclusion / approval by the Chinese FDA - I doubt any non-Chinese trial would meet that - thus you do restrict to China only - and therefore must state this; b) my understanding of TCM is that of a "multidisciplinary" approach - meaning you always have decoction, acupuncture etc. in various mixes - why that restriction? * missing data: I object to multiple imputation to treat missing data for the following reasons: a) the expected dataset (number of studies) will not be sufficiently large to allow imputation with sufficient statistical accuracy; b) you will run into the Simpsons paradox; c) baseline-differences may preclude meta-regression alltogether. * data-synthesis: please state the quantification of the ouctome measure(s) in more detail - e.g. you can transform to the log-hazard ratio scale (see Woods et al) as R is quite capable of that, you can stay with RR , etc. ... * statistical software: a) which R-extensions did you use? b) which stata-command-suite did you use? c) why did you use both software - they are both quite capable of doing the calcs alone? d) As far as I know, R does not produce SUCRA values (though quite valid substitutes) and stata does not do Bayesian NMA-models

REVIEWER	Yanling Zhao The Fifth Medical Center of General Hospital
REVIEW RETURNED	15-Mar-2020

GENERAL COMMENTS	In this manuscript, the author aims to assess and compare the effect of different TCMIs for HF using network meta-analysis (NMA) and further provide references for clinical decision-making. However, several points need clarify and further justification. There are given below: 1. Please add the diagnostic criteria of heart failure. 2. Some details are not specific enough, for example, it is unscientific that the inclusion criteria does not limit whether there are complications. 3. Which Chinese medicine injections were included specifically, and why? 4. It is recommended that the study be registered before meta-analysis. 5. In data analysis, Assessment of publication bias part, it is suggested to add the command code of R (version 3.6.1) and STATA (version 16.0). 6. It is recommended that the study be registered before meta-analysis. 7. The article did not explain some details, such as whether all papers that meet the inclusion criteria will be studied, and whether it will lead to un-analysis. If there is little literature to support a treatment, is it excluded still? 8. There are a number of vocabulary and grammar errors that need attention.

REVIEWER	Chuan Wang Shaanxi University of Chinese Medicine; China
REVIEW RETURNED	16-Mar-2020

GENERAL COMMENTS	The authors investigated the efficacy and safety of TCMIs in the treatment of HF. However, there are several questions to be addressed properly. 1. The author did not report the registry information of this review design on any platform. 2. Inclusion criteria for patients were unclear. 3. Types of interventions were unclear. 4. The primary outcomes need to be more detailed. Overall, the review has not been conducted very well. Major revisionis recommended.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Lutz Frankenstein
* type of participants: a) why restrict to pure CHF? b) how do you define "serious complications or other organic disease"? c) given the co-morbidity burden of CHF, wouldn't that severly truncate your population?
Response: Considering the comments of the reviewers, we realized that the previous description is indeed problematic. So we have modified the type of participants in the “inclusion criteria” and defined the diagnostic criteria for HF. Besides, we defined patients with serious complications or other organic diseases in detail in the "exclusion criteria", that is, “Participants are any of the following: the primary disease is congenital heart disease, pulmonary heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, systemic invasive disease, hyperthyroid heart disease, alcoholic myocardium disease, perinatal cardiomyopathy, drug-induced cardiomyopathy, Keshan disease. Participants are any of the following: heart failure with malignant arrhythmias, malignant tumors, hypothyroidism, severe liver and kidney dysfunction, or severe infections.” The

main corrections have been marked with red text in the manuscript.

* type of intervention: a) though you state "no restrictions to race" you still mandate inclusion / approval by the Chinese FDA - I doubt any non-Chinese trial would meet that - thus you do restrict to China only - and therefore must state this; b) my understanding of TCM is that of a "multidisciplinary" approach - meaning you always have decoction, acupuncture etc. in various mixes - why that restriction?
Response: a) Please let me explain this question. This sentence-“TCMIs must have been included in the Pharmacopoeia of the People's Republic of China or approved by the China Food and Drug Administration.”- is only used to limit the types of injections, in order to avoid the inclusion of those injections that are being developed but have not been officially approved by the Food and Drug Administration. This restriction does not apply to the race.
b) Indeed, as you said, TCM is a comprehensive treatment method that includes drug therapy and non-drug therapy. However, these different methods do not always have to be used in combination. They can be used alone. Traditional Chinese medicine injection (TCMI) is one of the drug therapies. The purpose of our research is to simply observe the clinical efficacy of injections rather than observe the mixed effects of multiple TCM treatment methods. Therefore, we excluded other TCM treatments such as decoctions, acupuncture, etc. To make the presentation clearer, we have added a supplementary explanation to the "exclusion criteria", that is, “Studies on the mixed efficacy of TCHIs combined with other TCM treatments will be excluded. For example, interventions have combined TCM decoctions, oral Chinese patent medicines, acupuncture, or something like that.”

* missing data: I object to multiple imputation to treat missing data for the following reasons: a) the expected dataset (number of studies) will not be sufficiently large to allow imputation with sufficient statistical accuracy; b) you will run into the Simpsons paradox; c) baseline-differences may preclude meta-regression alltogether.
Response: Thanks for this suggestion, we also realized that this problem might occur. Considering that studies with imbalanced baseline data will be excluded, we decided to remove this method. In addition, we have added an exclusion criterion, that is, "Studies with imbalanced or incomparable baseline data between the two groups will be excluded."

* data-synthesis: please state the quantification of the ouctome measure(s) in more detail - e.g. you can transform to the log-hazard ratio scale (see Woods et al) as R is quite capable of that, you can stay with RR , etc. ...
Response: We describe this in the data analysis, that is, “Dichotomous variables will be presented as the relative risk (RR) or odds ratio (OR) with a 95% credible interval (CrI). Continuous variables will be presented as the weight mean difference (WMD) with a 95% CrI.” But I am not sure if this is enough to answer the question you mentioned.

* statistical software: a) which R-extensions did you use? b) which stata-command-suite did you use? c) why did you use both software - they are both quite capable of doing the calcs alone? d) As far as I know, R does not produce SUCRA values (though quite valid substitutes) and stata does not do Bayesian NMA-models
Response: a) We plan to use the gemtc package in R (version 3.6.1) and we have supplemented it in the “data analysis”.
b) - c) Given the powerful capabilities of the R, we finally decided to use R for all data analysis.
d) Considering your comments, we deliberately checked the functions of the gemtc package and confirmed that there is a function called "rank. probability" that can be used to generate the probability distribution, and a function called "cumsum" can be further used to calculate SUCRA values.

Reviewer: 2
Reviewer Name: Yanling Zhao
1.Please add the diagnostic criteria of heart failure.
Response: We are very sorry because we forgot to cite a reference. We have defined the diagnostic criteria for HF and the relevant literature has been cited this time. The main corrections have been marked with red text in the manuscript.

2.Some details are not specific enough, for example, it is unscientific that the inclusion criteria does not limit whether there are complications.
Response: Considering the comments of the reviewers, we have modified the type of participants in the “inclusion criteria” and defined patients with serious complications or other organic diseases in detail in the "exclusion criteria", that is, “Participants are any of the following: the primary disease is congenital heart disease, pulmonary heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, systemic invasive disease, hyperthyroid heart disease, alcoholic myocardium disease, perinatal cardiomyopathy, drug-induced cardiomyopathy, Keshan disease. Participants are any of the following: heart failure with malignant arrhythmias, malignant tumors, hypothyroidism, severe liver and kidney dysfunction, or severe infections.”

3.Which Chinese medicine injections were included specifically, and why?
Response: We would like to explain the reason why the type of injection is not determined in advance. Because the purpose of our study was to systematically search for all eligible studies, we have no way to determine which injections should be included before the study began formally. But we have set strict inclusion and exclusion criteria for interventions.

4.It is recommended that the study be registered before meta-analysis.
Response: An application for registration of this study was submitted to the PROSPERO in January 2020, but it will take at least three months for it to be registered.

5.In data analysis, Assessment of publication bias part, it is suggested to add the command code of R (version 3.6.1) and STATA (version 16.0).
Response: Thanks for your suggestion. Given the powerful capabilities of the R, we finally decided to use R for all data analysis. So we plan to use the gemtc package in R (version 3.6.1) and we have supplemented it in the “data analysis”.

6.It is recommended that the study be registered before meta-analysis.
Response: An application for registration of this study was submitted to the PROSPERO in January 2020, but it will take at least three months for it to be registered.

7.The article did not explain some details, such as whether all papers that meet the inclusion criteria will be studied, and whether it will lead to un-analysis. If there is little literature to support a treatment, is it excluded still?
Response: Because our research purpose is to systematically and comprehensively search all related clinical RCTs, all studies that meet the inclusion and exclusion criteria will be included. This description, "The data are incomplete or incorrect, and the data cannot be used for synthesis." was added to the “exclusion criteria” to avoid un-analysis. To make the study design more detailed, this description, “All retrieved eligible TCMIs may be included in the study, but TCMIs without literature support will not be compared and ranked.” was added to the “exclusion criteria” and marked in red text.

8.There are a number of vocabulary and grammar errors that need attention.
Response: Thanks for your suggestion. We asked an English professional to help us correct the vocabulary and grammar errors in the manuscript. The word corrections have been marked with blue

text in the manuscript.

Reviewer: 3
Reviewer Name: Chuan Wang
1.The author did not report the registry information of this review design on any platform.
Response: I'm sorry that we are temporarily unable to provide registry information. An application for registration of this study was submitted to the PROSPERO in January 2020, but it will take at least three months for it to be registered.

2.Inclusion criteria for patients were unclear.
Response: Considering the comments of the reviewers, we have defined the diagnostic criteria for HF and the relevant literature has been cited in the "inclusion criteria" and marked in red text. Besides, we have defined patients with serious complications or other organic diseases in detail in the "exclusion criteria", that is, "Participants are any of the following: the primary disease is congenital heart disease, pulmonary heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, systemic invasive disease, hyperthyroid heart disease, alcoholic myocardium disease, perinatal cardiomyopathy, drug-induced cardiomyopathy, Keshan disease. Participants are any of the following: heart failure with malignant arrhythmias, malignant tumors, hypothyroidism, severe liver and kidney dysfunction, or severe infections." The main corrections have been marked with red text in the manuscript.

3.Types of interventions were unclear.
Response: We would like to explain the reason why the type of injection is not determined in advance. Because the purpose of our study was to systematically search for all eligible studies, we have no way to determine which injections should be included before the study began formally. But we have set stricter inclusion and exclusion criteria for interventions.

4.The primary outcomes need to be more detailed.
Response: Thanks for your suggestion. We have modified the primary outcomes to "all-cause mortality during different follow-up periods-eg 3 months; 6 months; 1 year or other periods" and "rehospitalization rate during different follow-up periods-eg 3 months; 6 months; 1 year or other periods".

We tried our best to improve the manuscript and made some changes to the manuscript. We appreciate the warm work of editor and reviewers earnestly and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions.
Thank you and best regards,
Shan-Shan Lin

VERSION 2 – REVIEW

REVIEWER	Lutz Frankenstein University of Heidelberg, Germany
REVIEW RETURNED	23-Jun-2020

GENERAL COMMENTS	the authors have addressed my comments in an acceptable way. My suggestions to them are:

	* while I completely understand why you mandate C-FDA approval, it still is quite unlikely that European or American studies will meet this criterion. It is conceivable that countries other than China pick up the TCM way and develop their own ideas. You should at leas acknowledge in "limitations" that your approach is "China-centred" - though presumably the vast majority of TCM and studies will come from China... * missing data: that's how I would do it, too. If your statistician is willing, you may repeat the main analysis with an imputed dataset as a sensitivity analysis and see what happens.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Lutz Frankenstein

Institution and Country: University of Heidelberg, Germany

Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below

the authors have addressed my comments in an acceptable way. My suggestions to them are:

* while I completely understand why you mandate C-FDA approval, it still is quite unlikely that European or American studies will meet this criterion. It is conceivable that countries other than China pick up the TCM way and develop their own ideas. You should at least acknowledge in "limitations" that your approach is "China-centred" - though presumably the vast majority of TCM and studies will come from China...

***Response*:** Thanks for your suggestion. We have added the limitations “Since most TCMIs and clinical trials will come from China, the conclusion may have certain limitations.” in the **Strengths and limitations of this study** section.

* missing data: that's how I would do it, too. If your statistician is willing, you may repeat the main analysis with an imputed dataset as a sensitivity analysis and see what happens.

***Response*:** Thanks for your suggestion. We have added the method, that is, “sensitivity analyses will be performed by repeating the main analysis with an imputed dataset using multiple imputation by chained equations.” in the **Dealing with missing data** section.

We tried our best to improve the manuscript and made some changes to the manuscript. We appreciate the warm work of editor and reviewers earnestly and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Thank you and best regards,

Shan-Shan Lin