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

TITLE (PROVISIONAL)	Comparison of the efficacy and acceptability of Chinese herbal medicine in adult patients with heart failure and reduced ejection fraction: study protocol for a systematic review and network meta-analysis
AUTHORS	LIU, Jing Lu, Jin Zhou, Kun Wan, Jie Li, Yan Cui, Xiao Gao, Qun Huang, Yan Li, Si Dong, Qiao Lin, Qian

VERSION 1 - REVIEW

REVIEWER	Iosief Abraha
REVIEW RETURNED	23-Jan-2017

GENERAL COMMENTS	This protocol proposes to perform a systematic review to evaluate the efficacy and acceptability of Chinese herbal medicine in adult patients with heart failure and reduced ejection fraction by systematically searching relevant articles in 10 databases. The strength of the review is that it will apply the methodology of the network meta-analysis to assess indirect and direct evidence from all alternative treatment options for the same condition. The protocol addresses an important clinical question but it needs a revision concerning the issue of risk of bias and other minor issues (please see below). In addition, the authors need to look at the paper by Bafeta et al (BMJ 2014;348:g1741) regarding the reporting issues of network meta-analyses to enhance the reporting of their future work. Page 5, line 5-14: the paragraph "… these trials yielded different results…" need referencing. Page 6, line 14; it looks like any non-randomized studies will be excluded. I suggest to refer to non-randomized than limiting to quasi-RCT. Line 39: the criteria need to be either specified in the text or described in a box Page 9; line 14 and 37: will the 4 reviewers act as 2 pairs of reviewers? Or are all the 4 reviewers going to screen/extract the same abstract/raw data?

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	Page 10: I would suggest not to base number of domains to judge the overall risk of bias. For example, performance bias will likely be present in all trials. As Chinese herbal medicine are non-pharmacological interventions (BMJ Open. 2015 Jan 27;5(1):e007488) I believe it is difficult to blind participants and investigators. In addition, the presence of an unclear or high risk of detection bias might not be important when the outcomes are objective (such as mortality or re-hospitalization; doi: 10.1371/journal.pone.0123090). In this regards, authors should discriminate between subjective and objective outcomes. Regarding selective outcome the authors need to consider the outcomes that are critical for the issue they are addressing.

REVIEWER	Wu, Xin Yin
REVIEW RETURNED	02-Mar-2017

GENERAL COMMENTS	This systematic review with network meta-analysis (NMA) aims to evaluate the comparative effectiveness of Chinese herbal medicine (CHM) for the treatment of heart failure and reduced ejection fraction. My comments is listed below. 1 By conducting NMA, we have to assume there is transitivity within the network. How will the author assess the assumption of transitivity before NMA? 2 How will routine treatment be defined? Will it include only one treatment or will it include a group of treatments? If the routine treatment include a group of treatments, will you consider them as one node in the network? Why or why not? 3 In the assessment of inconsistency between direct and indirect evidence, the author stated that "two or three methods will be used". Why did you choose two or three methods? If there are controversy results among different methods, how will you make conclusion? 4 The author gave the rule for summarizing a overall risk of bias for one trial in the risk of bias assessment part. However, I can not find the rule from Cochrane handbook, can you give a reference to support your rule for the summarizing of overall risk of bias?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. “Page 5, line 5-14: the paragraph “… these trials yielded different results…” need referencing.”
Response: According to reviewer’s suggestion, we have added references 7(Guicheng Xu, et al. Clinical trials of Qiliqiangxin capsule in the treatment of chronic congestive heart failure. Chin J Diffic and Complic Cas. 2008; 7(5):262-4.), 8(Zhengyang Yang, et al. Observation the effect of Qiliqiangxin capsule on heart failure with reduced ejection fraction. Chin Fore Med Treat. 2010; 5:113.), 9(Xiaowei Li, et al. Observation the effect of Qiliqiangxin decoction on 70 patients diagnosed as heart failure with reduced ejection fraction. 2010;32(1):71-2.) in manuscript.
2. “Page 6, line 14; it looks like any non-randomized studies will be excluded. I suggest to refer to non-randomized than limiting to quasi-RCT.”
Response: According to reviewer’s suggestion, we have changed ‘quasi-RCT’ to ‘non-RCT’.
3. “Line 39: the criteria need to be either specified in the text or described in a box.”

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Response: Sorry to say that we cannot figure out what the 'criteria' referred to by reviewer. Is it all criteria or any specific criteria (e.g., Types of studies, Types of participants)? If it referred to the all criteria, we believe that we have specified them in the text.
4. "Page 9; line 14 and 37: will the 4 reviewers act as 2 pairs of reviewers? Or are all the 4 reviewers going to screen/extract the same abstract/raw data?"
Response: We are very sorry for our negligence on making this point clearly. Here, we mean 4 reviewers acting as 2 pairs of reviewers and have corrected this error in the manuscript.
5. "Page 10: I would suggest not to base number of domains to judge the overall risk of bias. For example, performance bias will likely be present in all trials. As Chinese herbal medicine are non-pharmacological interventions (BMJ Open. 2015 Jan 27;5(1):e007488) I believe it is difficult to blind participants and investigators. In addition, the presence of an unclear or high risk of detection bias might not be important when the outcomes are objective (such as mortality or re-hospitalization; doi: 10.1371/journal.pone.0123090). In this regards, authors should discriminate between subjective and objective outcomes. Regarding selective outcome the authors need to consider the outcomes that are critical for the issue they are addressing."
Response: We are very sorry for our negligence on this point and appreciate reviewer's thoughtful suggestions. According to reviewer's suggestion, we have changed this paragraph to "As Chinese herbal medicine is difficult to blind participants, performance bias will likely be present in all trials. When it comes to objective outcomes such as all-cause mortality, performance bias and detection bias might not be so important that we can summarize this trial as low risk if bias of other remaining domains are ranked as low. However, for highly subjective outcomes such as quality–of-life score, we determine that both blinding of participants and outcome assessment are critical. High risk of bias for one or more key domains within such study will be evaluated as high risk of bias. In addition, regarding selective outcome, this domain will be ranked as 'low risk' unless the outcomes are critical for our issue, such as all-cause mortality, all-cause rehospitalization and acceptability."

Reviewer: 2
Reviewer Name: Wu, Xin Yin
1. "By conducting NMA, we have to assume there is transitivity within the network. How will the author assess the assumption of transitivity before NMA?"
Response: According to reviewer's suggestion, we added "to assure transitivity within the network, common comparator in a single node should be systematically or proportionally similar in some baseline characteristics, such as gender, age, co-morbidity, combined medication and HFrEF severity" in "Types of participants" section and "distribution with respect to potential effect modifiers (e.g., administration route, dose, frequency) among trials in one single node should be similar." in "Types of interventions" section.
2. "How will routine treatment be defined? Will it include only one treatment or will it include a group of treatments? If the routine treatment includes a group of treatments, will you consider them as one node in the network? Why or why not?"
Response: We define routine treatment as guideline-directed medical therapy (GDMT, e.g., ACE inhibitor, ARB, Beta blocker, Aldosterone antagonist and Hydralazine/nitrate) or inotropic drugs (e.g., Digaoxin), which may refer to only one treatment or a group of treatments. In our opinion, even if routine treatment includes a group of treatments, it can be considered as one node in the network because GDMTs underline similar mechanism in theory and before NMA, transitivity and homogeneity will be pre-satisfied.
3. "In the assessment of inconsistency between direct and indirect evidence, the author stated that "two or three methods will be used". Why did you choose two or three methods? If there are controversy results among different methods, how will you make conclusion?"
Response: According to reviewer's suggestion, we changed this statement as "three methods will be used". These three methods will assess inconsistency from three different perspectives, which are node-specific, loop-specific and global aspects. All these methods will serve for a more robust

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conclusion. If there are controversy results among different methods, we will make a comprehensive conclusion based on the ratio of results, heterogeneity and overall risk of bias.
4. “The author gave the rule for summarizing a overall risk of bias for one trial in the risk of bias assessment part. However, I can not find the rule from Cochrane handbook, can you give a reference to support your rule for the summarizing of overall risk of bias?”
Response: According to two reviewers’ suggestions, we have changed this paragraph to “As Chinese herbal medicine is difficult to blind participants, performance bias will likely be present in all trials. When it comes to objective outcomes such as all-cause mortality, performance bias and detection bias might not be so important that we can summarize this trial as low risk if bias of other remaining domains also being ranked as low. However, for highly subjective outcomes such as quality–of-life score, we decide that both blinding of participants and outcome assessment are critical. High risk of bias for one or more key domains within a study will be evaluated as high risk of bias. In addition, regarding selective outcome, this domain will be ranked as ‘low risk’ unless the outcomes are critical for our issue, such as all-cause mortality, all-cause rehospitalization and acceptability.”
Editorial Requests:
1. “The quality of English is currently not at the requisite standard for publication. Please thoroughly copy-edit the manuscript. We recommend consulting a native English speaker/ professional copy-editing service if possible.”
Response: Because of limited time and funds, we invited a postgraduate who majors in English to copy-edit our manuscript. If the quality of English is still not at the requisite standard for publication, please do not hesitate to tell us and we will try our best to make it right.
2. “Please provide a draft of the full search strategy for at least one database as a supplementary file and refer to this in the methods section.”
Response: We attached search strategy of EMBASE and CENTRAL to appendix 2 and referred to it in the method section.
3. “PRISMA-P Checklist Item 7: please clearly state your objective(s) at the end of the introduction section.”
Response: According to editorial request, we have changed the end of last paragraph of the “Backgroud” section to “To be specific, ……to estimate and rank the effectiveness and acceptability of all CHM or CHM plus routine treatment on HFrEF by comparing with routine treatment, placebo or CHM.”
4. “PRISMA-P Checklist Item 9: the literature search needs updating (it is over 12 months old now).”
Response: We have updated the literature search to March, 2017.
5. “PRISMA-P Checklist Item 13: please include a rationale for the outcomes selected or clarify where this is reported in the manuscript.”
Response: We have included a rational for the outcomes selected as reference 15 (Song Wen-Ting, et al. Chinese Medicine Shenfu injection for heart failure: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2012; 2012:713149.).
In addition, we tried our best to improve the manuscript and made some changes in the manuscript. These changes mainly focused on language issues and format, which will not influence the content of the protocol. And here we did not list the changes but marked in red in revised paper.

VERSION 2 – REVIEW

REVIEWER	Iosief Abraha
REVIEW RETURNED	06-May-2017

GENERAL COMMENTS	The changes performed are satisfactory. I have no other comment.

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REVIEWER	Xin Yin Wu
REVIEW RETURNED	17-May-2017

GENERAL COMMENTS	The authors have addressed majority of my comments. However, I do not agree to treat the routine treatment as one simple node if it includes various types of different treatments(guideline-directed medical therapy (GDMT, e.g., ACE inhibitor, ARB, Beta blocker, Aldosterone antagonist and Hydralazine/nitrate) or inotropic drugs (e.g., Digaoxin)). They will be considered as high level of clinical heterogeneity. According to the recommendation provided by Cochrane handbook, ignore the clinical heterogeneity should be considered as one typical example of combining orange and apple together.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Xin Yin Wu

1. “The authors have addressed majority of my comments. However, I do not agree to treat the routine treatment as one simple node if it includes various types of different treatments (guideline-directed medical therapy (GDMT, e.g., ACE inhibitor, ARB, Beta blocker, Aldosterone antagonist and Hydralazine/nitrate) or inotropic drugs (e.g., Digaoxin)). They will be considered as high level of clinical heterogeneity. According to the recommendation provided by Cochrane handbook, ignore the clinical heterogeneity should be considered as one typical example of combining orange and apple together.”
Response: We are very grateful to Professor Wu for her patient explanation and feel sorry for our lack of consideration. According to Pro. Wu’s suggestion, we changed this section to “We define routine treatment as GDMT (e.g., ACE inhibitor, ARB, Beta blocker, Aldosterone antagonist and Hydralazine/nitrate) or inotropic drugs (e.g., Digaoxin), which refer to only one GDMT”

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