

## 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

<b>TITLE (PROVISIONAL)</b>	Comparative Effectiveness of Six Chinese Herb Formulas for Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Protocol for Systematic Review and Network Meta-analysis
<b>AUTHORS</b>	Liu, Shaonan; Chen, Jing; He, Yihan; Wu, Lei; Lai, Jiaqi; Zuo, Jinhong; Yang, Lihong; Guo, Xinfeng

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Rita Pavasini Cardiology Unit, Azienda Ospedaliero Universitaria S.Anna, Ferrara, Italy
<b>REVIEW RETURNED</b>	14-Apr-2017

<b>GENERAL COMMENTS</b>	<p>This is a Protocol for a network meta-analysis about the effectiveness of 6 Chinese herbs for AECOPD. This will be an interesting study. I have only minor suggestions:</p> <ul style="list-style-type: none"><li>- Did you include only reference from peer-reviewed journal? Or also abstract or other material?</li><li>- Which was the criterion for COPD diagnosis? Did you select only study with COPD confirmed by spirometry?</li><li>- Could you include also hospital readmission for acute exacerbation of COPD as outcome?</li><li>- Why do you use only a random effect? According the degree of heterogeneity expressed as I<sup>2</sup>, you can use a fixed effect if I<sup>2</sup> is &lt;50% and a random effect if I<sup>2</sup> is &gt; 50%.</li><li>- Which statistical test will you use to quantify the presence of publication bias?</li><li>- Personally I would not include the empty figure of the outline of the search strategy, I would eliminate it.</li><li>- I would write a paragraph as "discussion" with the aim and expectation from the results of this meta-analysis.</li></ul>
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<b>REVIEWER</b>	Akimichi Nagashima Respiratory Medicine, Saiseikai Yokohamashi Nanbu Hospital, JAPAN
<b>REVIEW RETURNED</b>	19-May-2017

<b>GENERAL COMMENTS</b>	<p>The authors studied the best combination medicine from six Chinese herbal formulas in exacerbation of COPD. This study dealt with an important issue in respiratory medicine. COPD exacerbation is common in clinical situation and many physicians are interested in reducing the risk of it. Network meta-analysis is one of the best methods to compare some therapies at once. Although the study is well designed, few issues should be clarified before the publication.</p>
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	<p><b>Major Comments</b></p> <ol style="list-style-type: none"> <li>1. Chinese herbal therapies are not commonly accepted as a standard treatment especially in western country. Therefore, the authors should address the detailed effects of the six Chinese herbal therapies, and the benefits of adding Chinese herb formulas to the standard therapies in Introduction.</li> <li>2. This study focuses on the efficacy regarding recovery from AECOPD through assessment of FEV1.0, arterial blood gas, and the length in hospital. Thus, it does not focus on prevention of AECOPD, authors should describe in Introduction paragraph about concrete targets in this study.</li> <li>3. Lung function during admission in hospital is not suitable for good index recovering from COPD. Symptoms including dyspnea, cough, or sputum and frequency of exacerbation may be better parameters.</li> </ol> <p><b>Minor Comments</b></p> <ol style="list-style-type: none"> <li>1. Page 4, "Also, the clinical practice.....these pharmacotherapies." I am afraid it is difficult to understand what authors are meaning, please replace it with other sentence.</li> <li>2. Page 6, " If the heterogeneity..., treatment duration et al." Authors should describe all of factors, or other expression will be better than "...et al".</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. Did you include only reference from peer-reviewed journal? Or also abstract or other material?

Response : We also include conference papers, thesis or dissertations. We will screen the abstract, and exclude it if not report enough information. All the screening procedure will present in PRISMA flow chart.

2. Which was the criterion for COPD diagnosis? Did you select only study with COPD confirmed by spirometry?

Response : COPD should be confirmed according to the standard diagnostic criteria including the Global Initiative for Chronic Obstructive Lung Disease [GOLD]; the British Thoracic Society, the American Thoracic Society, the European Respiratory Society or Chinese COPD guideline. All these criterions contain the diagnosis of spirometry. We only include the studies with specified diagnostic criteria. The details of diagnosis were revised in the participants section.

3. Could you include also hospital readmission for acute exacerbation of COPD as outcome?

Response: This outcome was included.

4. Why do you use only a random effect? According the degree of heterogeneity expressed as I<sup>2</sup>, you can use a fixed effect if I<sup>2</sup> is <50% and a random effect if I<sup>2</sup> is > 50%.

Response: It has mentioned that the choice between a fixed-effect and a random-effects meta-analysis should never be made on the basis of a statistical test for heterogeneity in Cochrane handbook (see section 9.4.3). The random effect model is conservative method that it accounts for both within-study and between-study variability. The relative reference list as below:

1.C Tufanaru, Z Munn, M Stephenson, E Aromataris. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. International journal of evidence-based healthcare , 2015 , 13 (3) :196

5. Which statistical test will you use to quantify the presence of publication bias?

Response: We will conduct egger's regression test to detect the potential publication bias and give

further discussion.

6. Personally I would not include the empty figure of the outline of the search strategy, I would eliminate it.

Response: Thanks. We prefer to keep this figure to show the screening procedure.

7. I would write a paragraph as “discussion” with the aim and expectation from the results of this meta-analysis.

Response: The description of discussion section was added.

#### Reviewer 2

1. Chinese herbal therapies are not commonly accepted as a standard treatment especially in western country. Therefore, the authors should address the detailed effects of the six Chinese herbal therapies, and the benefits of adding Chinese herb formulas to the standard therapies in Introduction.  
Response: We deeply appreciate your valuable suggestions. A few sentences were added in the introduction section.

2. This study focuses on the efficacy regarding recovery from AECOPD through assessment of FEV1.0, arterial blood gas, and the length in hospital. Thus, it does not focus on prevention of AECOPD, authors should describe in Introduction paragraph about concrete targets in this study.  
Response: Thanks. After group discussion, we add hospital readmission for acute exacerbation as the secondary outcome for our research.

3. Lung function during admission in hospital is not suitable for good index recovering from COPD. Symptoms including dyspnea, cough, or sputum and frequency of exacerbation may be better parameters.  
Response: We have included dyspnea in our secondary outcome. Also, we added effective rate outcome, which is judged according to the improvement of clinical symptoms, such as cough, sputum and dyspnea. Details were revised in the outcome section.

#### Minor Comments

1. Page 4, “Also, the clinical practice.....these pharmacotherapies.” I am afraid it is difficult to understand what authors are meaning, please replace it with other sentence.

Response : The sentence was revised to “Moreover, these therapies have been associated with some side effects such as tremor, hyperglycaemia, candidiasis and antibiotic resistance. Clinicians should balance the effectiveness and safety of these pharmaceutical interventions for patients.”

2. Page 6,” If the heterogeneity..., treatment duration et al.” Authors should describe all of factors, or other expression will be better than “...et al”.

Response: “et al” was deleted. No further information was added.

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

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Rita Pavasini Azienda Ospedaliero Universitaria S.Anna, Ferrara, Italy
<b>REVIEW RETURNED</b>	22-Jun-2017

<b>GENERAL COMMENTS</b>	Authors well addressed all the questions raised. This is a very complete and well done protocol for meta-analysis.
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