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>Study protocol for a single-blind, placebo-controlled randomized trial of Tianjiu effects in patients with intradialytic hypotension</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Tsai, Ming-Yen; Su, Yu-Jen; Ng, Hwee-Yeong; Chen, Shih-Yu; Huang, Yu-Chuen; Wu, Chien-Hsing; Chen, Yung-Hsiang</td>
</tr>
</tbody>
</table>

**VERSION 1 - REVIEW**

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Len Usvyat</th>
<th>Fresenius Medical Care North America</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>03-Nov-2015</td>
<td></td>
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</table>

**GENERAL COMMENTS**

This is a well written and interesting study. My main concern is whether this is something BMJ is interested in publishing – there are no results and the information provided is only about how the study will be conducted.

I do also have some specific points about the study:

1. It appears the main objective of the study is to determine the impact on IDH but that is not listed as primary outcome of interest. Somehow ultrafiltration achieved appears to be the main outcome
2. It's unclear how the patients will be enrolled to be in the study. It states that it will be based on IDH and then it states that it will be based on KDOQI guidelines
3. It appears that the patients will be chosen through advertising? This is odd that they will be coming from different centers
4. Are there any matching algorithms to assure that both arms have similar patients?
5. How do you assure that patients receiving this treatment will not realize they are getting Tianjiu therapy because of the odor associated with it?
6. Why do you standardize the prescription? That may introduce some bias into the results

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Xingjiang Xiong</th>
<th>Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>27-Dec-2015</td>
<td></td>
</tr>
</tbody>
</table>

**GENERAL COMMENTS**

It is an interesting protocol of Tianjiu in patients with intradialytic hypotension. However, some significant drawbacks were identified in this article.

Firstly, as stated in the article, "Accumulating evidence shows that applying Tianjiu to specific acupoints has a therapeutic effect on clinical symptoms and quality of life in HD patients.22 23", please ensure that whether these 2 articles investigated the effect of Tianjiu on HD patients.
Secondly, comprehensive literature searches were conducted in 4 main Chinese databases (including CNKI, CBM, VIP, and Wanfang) with “Tianjiu” and “HD” as keywords. However, no articles could be found. That is to say, no evidence of Tianjiu for human healthcare could be drew based on the published literature.

Thirdly, what is the basis for the choice of course of treatment? In my opinion, as IDH is the chronic disease, maybe a longer treatment duration is more appropriate.

Fourthly, the pathogenesis of symptomatic IDH is related to not only the deficiency of qi, blood, yin and yang, but also some pathological products accumulated in the body, e.g. qi stagnation, blood stasis, and phlegm. In my opinion, it shouldn’t be ascribed to the deficiency of yang briefly.

Fifthly, only yongquan and guanyuan were selected. According to the characteristic of IDH, may be more acupoints (e.g. zusanli, sanyinjiao, et. al) were needed.

**Reviewer: 1 Len Usvyat**

This is a well written and interesting study.
I do also have some specific points about the study:

1. It appears the main objective of the study is to determine the impact on IDH but that is not listed as primary outcome of interest. Somehow ultrafiltration achieved appears to be the main outcome
Re: The majority of patients with ESRD are treated with HD to regulate their fluid balance and other native kidney functions. When patients experience IDH, HD is difficult to process or complete. We need to increase the dry-weight and reduce the ultrafilter (UF), but at the risk of volume overload and cardiovascular events. If we increase the ultrafiltration volume to help with rapid fluid removal, IDH can more easily occur. This is a circular cause and consequence. Thus, the UF achieved is an important index for the effects of many interventions to determine the condition and BP during each HD session. A higher UF achieved represents that more IDH episodes will occur. That is why we chose the % of target ultrafiltration as the primary endpoint. Knoll et al. [1] also adopted the index of the primary endpoint to compare albumin versus saline for the treatment of IDH.

Ref.

2. It’s unclear how the patients will be enrolled to be in the study. It states that it will be based on IDH and then it states that it will be based on KDOQI guidelines
Re: KDOQI guidelines provide physicians with information on HD complications, definition, risk factors, dialysate electrolyte modeling, and therapeutic principles. There are many different definitions of IDH; however, the one in our trial is mainly based on the KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. (http://www2.kidney.org/professionals/kdoqi/guidelines_cvd/intradialytic.htm) In addition, other participants’ conditions and the study setting are described in our study.

3. It appears that the patients will be chosen through advertisings? This is odd that they will be coming from different centers
Re: We apologize for the confusion. They will not be from different centers; all patients, distributed in 3 stations on 2 floors, will be enrolled in our KCGMH center. We have revised the sentence from “plan to recruit participants via advertisements such as websites, ....” to “plan to recruit participants via
advertisements in our HD units."

4. Are there any matching algorithms to assure that both arms have similar patients?
Re: Thank for you pointing that out. We have revised “A block randomization procedure will be employed to ensure that group allocation is equal” to “A block randomization procedure (age, comorbidities such as cardiovascular disease or diabetes mellitus) will be employed to ensure that group allocation is equal and that the characteristics of the trial subjects are similar” in the Study design, 2nd paragraph, line 8-10.

5. How do you assure that patients receiving this treatment will not realize they are getting Tianjiu therapy because of the odor associated with it?
Re: Thank you for raising an important point. Indeed, Tianjiu and placebo (clay) patches do smell different. The Tianjiu patch has a light fragrance of herbs when you are close to it. We adopt 3 methods to prevent patients from identifying the type of patch.
(1) Only patients who have never received Tianjiu before participating in this study will be included (see in Participants, line 2-3).
(2) The HD nurse will be encouraged to supervise participants and to prevent them from touching these patches during each HD session (see in Intervention, Treatment group and placebo group, line 9-11).
(3) The patches will be applied and removed by research assistants (see in Intervention, Treatment group and placebo group, line 11-12).

6. Why do you standardize the prescription? That may introduce some bias into the results
Re: Quality control is provided. All herbs were purchased from Sheng Chang Pharmaceutical Co., Ltd and can be preserved for 2 years. The paste will be produced by the Chinese Medicine Pharmacy of KCGMH according to a standard procedure on the day of use. Please see Interventions, Prescription and preparation of the Tianjiu paste, line 2-9.

**Reviewer: 2 Xingjiang Xiong**

It is an interesting protocol of Tianjiu in patients with intradialytic hypotension. However, some significant drawbacks were identified in this article.

Firstly, as stated in the article, "Accumulating evidence shows that applying Tianjiu to specific acupoints has a therapeutic effect on clinical symptoms and quality of life in HD patients.22 23", please ensure that whether these 2 articles investigated the effect of Tianjiu on HD patients.
Re: The references [22, 23], published in China, mentioned the effects of moxibustion rather than Tianjiu for HD patients. To make the statement more accurate, we have adjusted the sequence of the two sentences and rewritten them as follows: "Accumulating evidence shows that applying moxibustion to specific acupoints has a therapeutic effect on clinical symptoms and quality of life in HD patients [22, 23]. Tianjiu, one moxibustion therapy, also features a stimulating effect. Therefore, it should make the Yang-Qi abundant, blood circulation strong, and autonomic nerve activity smooth and harmonized in HD patients."

Secondly, comprehensive literature searches were conducted in 4 main Chinese databases (including CNKI, CBM, VIP, and Wanfang) with "Tianjiu" and "HD" as keywords. However, no articles could be found. That is to say, no evidence of Tianjiu for human healthcare could be drew based on the published literature.
Re: As described in the INTRODUCTION, 3rd paragraph, there are many another names for Tianjiu therapy, including "crude herb moxibustion", "auto-moxibustion", "herbal acupoint paste", and "cold moxibustion therapy". Therefore, we searched for the unique TCM therapy in those databases. Most
studies of Tianjiu therapy focus on chronic asthma and allergic rhinitis. In our clinical experience, this treatment can be applied for fatigue and chronic diseases such as colitis, uremia, COPD, and heart failure. Therefore, the objective of this study is to explore the new indications of Tianjiu therapy and report its efficacy.

Thirdly, what is the basis for the choice of course of treatment? In my opinion, as IDH is the chronic disease, maybe a longer treatment duration is more appropriate.

Re: Most research on IDH [1-3] suggests intervention in each HD session in 4-week courses. This is why we designed the experimental course to include a baseline period of 1 week, a treatment period of 4 weeks, and a follow-up period of 2 weeks. We have added your useful suggestions (points 3-5) to our Discussion, paragraph 2, line 16-19.

Ref.

Fourthly, the pathogenesis of symptomatic IDH is related to not only the deficiency of qi, blood, yin and yang, but also some pathological products accumulated in the body, e.g. qi stagnation, blood stasis, and phlegm. In my opinion, it shouldn't be ascribed to the deficiency of yang briefly.

Re: According the Chen report, there are 6 syndromes in HD patients, including Chi deficiency of Spleen and Kidney (CDSK), Yang deficiency of Spleen and Kidney (YDSK), Yin deficiency of Liver and Kidney (YDLK), deficiencies of Chi and Yin (DCY), deficiencies of Yin and Yang (DYY), and Non-deficiency (ND). The YDSK and DYY types of HD patients tend to be older and have longer dialysis periods, intelligence impairment, and malnutrition [1]. Wu reported in 2010 that along with the progress of HD, the TCM syndrome will change from qi-deficiency to yang-deficiency and further to both yin-yang deficiency, while in the superficial syndromes it will turn from turbid-damp to blood-stasis [2]. Our study protocol does not involve this issue because no studies to date have confirmed the TCM syndrome for IDH patients. However, this is an important viewpoint and can provide us a direction for future study. We have mentioned it in Discussion, 2nd paragraph, line 16-19. Thank you for your kindly advice.

Ref.

Fifthly, only yongquan and guanyuan were selected. According to the characteristic of IDH, may be more acupoints (e.g. zusanli, sanyinjiao, et. al) were needed.

Re: We appreciate your valuable suggestion; indeed, more acupoints were applied in some studies and a book [1-3]. Under the national health insurance system in Taiwan, however, the herbal paste can be applied to only 3-4 acupoints in each treatment. We will first complete the trial of Tianjiu therapy on bilateral KI1 and CV4 and then evaluate the need for more acupoints. In consideration of this point, we have added the sentence “Other assessments including more suitable acupoint applications, long-term therapeutic courses, and data on the efficacy of different TCM treatments in IDH patients will also be considered in a subsequent study” (see Discussion, 2nd paragraph, line 16-19).
Ref.

**GENERAL COMMENTS**
The authors have successfully addressed all the comments I noted previously. Some minor points:

1. page 7: Suggest either adding commas around "after identification by a nephrologist" OR rephrasing: "Eligible participants will be identified by a nephrologist as meeting the criteria of IDH in this study and will be randomly and equally assigned to the Tianjiu group or the placebo group at a 1:1 ratio."

2. page 9, line 7 is a redundant sentence and should be removed

3. page 10, line 36: replace comma with "and": "...will be selected based on evaluation of moxibustion literature and will be disinfected using 75% alcohol."

4. page 11, line 15: Suggest: "Fresh ginger juice will be added to these herbs..."

5. page 11, line 18: If the study goes through July 2016, it is slightly more than 2 years.

6. page 12, line 42: Suggest "...the use of the Trendelenburg position,..."

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**VERSION 2 – REVIEW**

**REVIEWER**
Len Usvyat  
Fresenius Medical Care

**REVIEW RETURNED**
03-Feb-2016

**GENERAL COMMENTS**
The authors have successfully addressed all the comments I noted previously. Some minor points:

1. page 7: Suggest either adding commas around "after identification by a nephrologist" OR rephrasing: "Eligible participants will be identified by a nephrologist as meeting the criteria of IDH in this study and will be randomly and equally assigned to the Tianjiu group or the placebo group at a 1:1 ratio."

2. page 9, line 7 is a redundant sentence and should be removed

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5. page 11, line 18: If the study goes through July 2016, it is slightly more than 2 years.

6. page 12, line 42: Suggest "...the use of the Trendelenburg position,..."

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**REVIEWER**
Xingjiang Xiong  
Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

**REVIEW RETURNED**
23-Jan-2016

**GENERAL COMMENTS**
All questions have been answered. It is a good revision.

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**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1 Len Usvyat

The authors have successfully addressed all the comments I noted previously. Some minor points:

1. page 7: Suggest either adding commas around "after identification by a nephrologist" OR
rephrasing: "Eligible participants will be identified by a nephrologist as meeting the criteria of IDH in this study and will be randomly and equally assigned to the Tianjiu group or the placebo group at a 1:1 ratio."

Re: Thank your suggestion. We have revised “Eligible participants meeting the criteria of IDH in this study after identification by a nephrologist will be randomly and equally assigned to the Tianjiu group or the placebo group at a 1:1 ratio.” to “Eligible participants will be identified by a nephrologist as meeting the criteria of IDH in this study and will be randomly and equally assigned to the Tianjiu group or the placebo group at a 1:1 ratio.”

2. page 9. line 7 is a redundant sentence and should be removed
Re: This sentence was similar to previous paragraph as you have said. So we decide to delete “During the entire study period, participants will be free to withdraw from the study at any stage without any consequences.” Thank you for reminding me.

3. page 10. line 36: replace comma with "and": "...will be selected based on evaluation of moxibustion literature and will be disinfected using 75% alcohol."
Re: We have replaced comma with "and: in page 10, line 36. The revised sentence is “…will be selected based on evaluation of moxibustion literature and will be disinfected using 75% alcohol.”

4. page 11. line 15: Suggest: "Fresh ginger juice will be added to these herbs..."
Re: “To these herbs will be added fresh ginger juice in a ratio of 1:1 before use” have been revised to “Fresh ginger juice will be added to these herbs in a ratio of 1:1 before use.”

5. page 11. line 18: If the study goes through July 2016, it is slightly more than 2 years.
Re: “All herbs were provided by Sheng Chang Pharmaceutical Co., Ltd. in June 2014 and can be refrigerated for up to 2 years” have been revised to “All herbs were provided by Sheng Chang Pharmaceutical Co., Ltd. in June 2014 and can be refrigerated more than 2 years.”

6. page 12. line 42: Suggest "...the use of the Trendelenburg position,..."
Re: We have revised “IDH-related interventions will be defined as the Trendelenburg position,...” to “IDH-related interventions will be defined as the use of Trendelenburg position,...” Thank for your above detailed comment.
Study protocol for a single-blind, placebo-controlled randomised trial of Tianjiu effects in patients with intradialytic hypotension

Ming-Yen Tsai, Yu-Jen Su, Hwee-Yeong Ng, Shih-Yu Chen, Yu-Chuen Huang, Chien-Hsing Wu and Yung-Hsiang Chen

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doi: 10.1136/bmjopen-2015-009976

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