PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Oral Chinese Herbal Medicine for Psoriasis Vulgaris: Protocol for a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial
AUTHORS	Deng, Jingwen; Yao, Danni; Lu, Chuan-jian; Wen, Zehuai; Yan, YuHong; He, Ziyang; Wu, Huimei; Deng, Hao

VERSION 1 – REVIEW

REVIEWER	Robert Gniadecki University of Alberta, Canada
REVIEW RETURNED	02-Oct-2016

GENERAL COMMENTS	It is a clear, well written protocol. I have the following questions: 1. Regarding the primary outcome. The authors state that "The primary outcome is reduction of PASI score. PASI score of patients will be assessed every 2 weeks during the treatment period and every 4 weeks in the follow-up period. Target lesions will be recorded as digital photo by SLR cameras in every visit." I do not understand why target lesion photography is included in the primary outcome. Second, when is the PASI reduction calculated as a primary outcome? Is there a specific time point or mean decrease between week 2 and 4.? 2. The study should also be registered at clinicaltrials.gov 3. Do placebo pills resemble the active treatment?

REVIEWER	Joanna Bartosinska Dep. of Dermatology, Venereology and Paediatric Dermatology Medical University of Lublin, Poland
REVIEW RETURNED	23-Oct-2016

GENERAL COMMENTS	The manuscript is the description of the study/trial protocol. It does not contain any study results. What is the aim of the study? In my oppinion the manuscript could be published after the study is finished (with final results and conclusions) or it should contain some preliminary results. The authors are going to include 556 psoriatic patients, however, till now they have recruited 53 participants. In the Background and Disscusion the authors have included some information about psoriasis pathogenesis and symptoms, however, explanations on the possible mechanism of action of the Chinese

	formulation on psoriasis symptoms and psoriasis co-morbidities are missing. Some grammar mistakes should be corrected.

REVIEWER	Ying Zhang Beijing University of Chinese Medicine, Beijing, China Beijing University of Chinese Medicine, Beijing, China
REVIEW RETURNED	19-Dec-2016

GENERAL COMMENTS	This is a well-designed double-blind and double dummy RCT. As a protocol, it reported this trial according to SPIRIT and CONSORT. The items reported in this protocol are very clearly and followed a good practice. Some paragraphs should be more rigorous. 1. Last paragraph in BACKGROUND: ..... Therefore, a rigorously designed randomized controlled trial to determine whether PSORI-CM01 is more effective than Yinxieling tablet…… 2. Inclusion criteria (3), PASI between 3 and 30, BSA less than 30%. What kind of patients will be included in this trial, the disease severity should be stated in protocol. For example, in the DESIGN part. 3. PRIMARY OUTCOME: the only primary outcome is the reduction of PASI score. But in the abstract, it were stated as the following “the primary outcome is reduction of psoriasis area and severity index score”. Please make them be consistency. In the meanwhile, for primary outcome, the primary time point should also be stated in protocol. 4. STRENGTHS AND LIMATATINS OF THIS STUDY: Please don’t use the word ”disinctive”. The last paragraph but one: please don’t use the word “first”. As a scientific research, knowing is limitless. We never know how much we don’t know. 5. SAMPLE SIZE: primary time point for primary outcome should be stated. The margin of equivalence was omitted in text? I didn’t find it. Please add it to make sure the sample size is appropriate. 6. RANDOMIZATION AND ALLOCATION: As the stratified block randomization will be used, please give the factor(s) which had been regarded as a stratification factor(s). 7. For Chinese medicine, double-dummy is often difficult to be realized in clinical practice because of its complicated flavor, color and odor. Please show the photos for both arms if possible. 8. STATISTICAL ANALYSIS: For ANOVA, I can’t figure out what kind of comparison should use it, may be ANCOVA will be more appropriate. If you mean repeated measure ANOVA, I feel that’s OK. 9. ADVERSE EVENTS: I think “changes from baseline of PASI” is secondary outcome. But I need authors’ confirmation. 10. DATA MANAGEMENT: Please give the name of CRO, as it is also an important collaborator of this trial. 11. TRIAL STATUS: Why only 53 patients (10% of target sample size) were recruited in two years? What’s the recruiting plan for this trial in the coming years.

REVIEWER	Mahmoud Rafieian-Kopaei Shahrekord University of Medical Sciences, Iran
REVIEW RETURNED	11-Jan-2017

GENERAL COMMENTS	The manuscript is not sound enough and does not provide enough

	novelty to be published in BMJ Open.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Robert Gniadecki
Institution and Country: University of Alberta, Canada
Please state any competing interests: None declared

Please leave your comments for the authors below

It is a clear, well written protocol. I have the following questions:

1. Regarding the primary outcome. The authors state that "The primary outcome is reduction of PASI score. PASI score of patients will be assessed every 2 weeks during the treatment period and every 4 weeks in the follow-up period. Target lesions will be recorded as digital photo by SLR cameras in every visit." I do not understand why target lesion photography is included in the primary outcome. Second, when is the PASI reduction calculated as a primary outcome? Is there a specific time point or mean decrease between week 2 and 4.?
Answer: We agree that it was improper that target lesion photography mentioned in the primary outcome. We have removed this phase from primary outcome description and insert into Design section. The PASI reduction calculated at 12 weeks was considered as the primary outcome. We are sorry we did not clarify it clearly before. We have modified the description in Primary outcome section.

2. The study should also be registered at clinicaltrials.gov
Answer: Thank you for your kindly reminder. To meet WHO requirements for transparency and publication it is only necessary for your trial to be to registered once, in either a Primary Registry or an ICMJE approved registry. We have registered this study in Chinese Clinical Trial Registry (ChiCTR) which had been assigned to be the representative registry of China to join WHO ICTRP in 2007. We may not register this study at clinicaltrials.gov for avoiding duplication registration.

3. Do placebo pills resemble the active treatment?
Answer: Yes, the main ingredients of placebo granules and placebo tablets are maltodextrin, lactose, and a natural edible pigment, are similar to the PSORI-CM01 granules and Yinxieling tablets in appearance, weight, and taste. The detail was stated at Test drugs and blinding section.

Reviewer: 2
Reviewer Name: Joanna Bartosinska
Institution and Country: Dep. of Dermatology, Venereology and Paediatric Dermatology Medical University of Lublin, Poland
Please state any competing interests: None declared

Please leave your comments for the authors below

The manuscript is the description of the study/trial protocol. It does not contain any study results. What is the aim of the study?
Answer: Yes, it is just a trial protocol without study results.
The aim of this study is to find out whether the PSORI-CM01 is more effective for psoriasis than the compared with original Yinxieling.

In my oppinion the manuscript could be published after the study is finished (with final results and conclusions) or it should contain some preliminary results. The authors are going to include 556 psoriatic patients, however, till now they have recruited 53 participants.
Answer: Protocol manuscript is for reporting planned or ongoing research study. Study protocols publishing enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. If data collection is complete, BMJ Open will not consider the manuscript.

In the Background and Disscusion the authors have included some information about psoriasis pathogenesis and symptoms, however, explanations on the possible mechanism of action of the Chinese formulation on psoriasis symptoms and psoriasis co-morbidities are missing.
Answer: Thank you for your advice. Our previous study showed PSORI-CM01 could reduce keratinocyte proliferation in vitro and inhibit epidermal hyperplasia in imiquimod-induced psoriasis-form mouse model. PSORI-CM01 formula could also affect the IL-17/IL-23 axis and inhibited the expression of cytokines and chemokines, improve inflammatory in dermic microenvironment. We have added these explanations in Background section.

Some grammar mistakes should be corrected.
Answer: We tried our best to improve the manuscript and made some changes on grammar in the manuscript. And we had sent the manuscript to AJE (American Journal Experts) for language service before submitting the revised version. Once again, thank you very much for your comments and suggestions.

Reviewer: 3
Reviewer Name: Ying Zhang
Institution and Country: Beijing University of Chinese Medicine, Beijing, China
Please state any competing interests: Beijing University of Chinese Medicine, Beijing, China

Please leave your comments for the authors below

This is a well-designed double-blind and double dummy RCT. As a protocol, it reported this trial according to SPIRIT and CONSORT. The items reported in this protocol are very clearly and followed a good practice.
Some paragraphs should be more rigorous.

1. Last paragraph in BACKGROUND: ..... Therefore, a rigorously designed randomized controlled trial to determine whether PSORI-CM01 is more effective than Yinxieling tablet……
Answer: We would like to thank the reviewer for the comments about the paragraphs of our manuscript. It is true that some sentences need to be more rigorous. We had sent the manuscript to AJE (American Journal Experts) for language service before submitting the revised version.

2. Inclusion criteria (3), PASI between 3 and 30, BSA less than 30%. What kind of patients will be included in this trial, the disease severity should be stated in protocol. For example, in the DESIGN part.
Answer: We recruited patients from 3 to 30 in PASI score. It contained mild, moderate and severe in psoriasis severity. In clinical observation, we noticed that the mild and moderate patients responded PSORI-CM01 formula better than patients in severe psoriasis. We also tended to recruit patients in mild and moderate psoriasis. But considered the sample size was more than 500. We had to expand the inclusion criteria in disease severity.

3. PRIMARY OUTCOME: the only primary outcome is the reduction of PASI score. But in the

abstract, it were stated as the following “the primary outcome is reduction of psoriasis area and severity index score”. Please make them be consistency.
In the meanwhile, for primary outcome, the primary time point should also be stated in protocol.
Answer: PASI is abbreviation of psoriasis area and severity index. In the abstract, the first time that the phrase appeared, we used “psoriasis area and severity index” instead of PASI. Abbreviations and acronyms are often defined the first time they are used and then used throughout the remainder of the manuscript.
We agree that the PASI reduction calculated at 12 weeks should be considered as the primary outcome. We are sorry we did not clarify it clearly before. We have modified the description in Primary outcome section.

4. STRENGTHS AND LIMATATINS OF THIS STUDY: Please don’t use the word ”disinctive”. The last paragraph but one: please don’t use the word “first”. As a scientific research, knowing is limitless. We never know how much we don’t know.
Answer: We tend to use “distinctive” to emphasize TCM characteristics in this double dummy trial for comparing clinical effect of Chinese medicine treatment before and after optimization and simplification. However, it was an improper use of words. It was also inappropriate that use the word “first” to describe a study. We modified the infelicitous sentences in the revised manuscript. Once again, thank you very much for your kindly reminder.

5. SAMPLE SIZE: primary time point for primary outcome should be stated. The margin of equivalence was omitted in text? I didn’t find it. Please add it to make sure the sample size is appropriate.
Answer: Thank you for your reminder. We have added the primary time point and equivalence formula in the Primary outcome section.

6. RANDOMIZATION AND ALLOCATION: As the stratified block randomization will be used, please give the factor(s) which had been regarded as a stratification factor(s).
Answer: In the setting of the stratified block randomization, center is regarded as the stratification factor.

7. For Chinese medicine, double-dummy is often difficult to be realized in clinical practice because of its complicated flavor, color and odor. Please show the photos for both arms if possible.
Answer: Here are the photos for Yingxieling tablet and PSORI-CM01 granule (Left: active treatment; Right:placebo).

The second picture, Yingxieling tablet is darker than placebo because herb composition be affected with damp (We are sorry we use expired drug for photo because all drug and placebo under guarantee are allocated random number. We do not know the blind codes now):

8. STATISTICAL ANALYSIS: For ANOVA, I can’t figure out what kind of comparison should use it, may be ANCOVA will be more appropriate. If you mean repeated measure ANOVA, I feel that’s OK.
Answer: For the comparison of the PASI scores, a continuous variable, we will use ANOVA to analyze the treatment effect and time effect. Because it is repeated measures analysis of variance change from baseline (PASI score of patients will be assessed every 2 weeks during the treatment period and every 4 weeks in the follow-up period).

9. ADVERSE EVENTS: I think “changes from baseline of PASI” is secondary outcome. But I need authors’ confirmation.
Answer: Yes, we agree that“changes from baseline of PASI”is an outcome. We have deleted this phrase from Adverse events section.

10. DATA MANAGEMENT: Please give the name of CRO, as it is also an important collaborator of this trial.
Answer: The monitoring tasks of this trial will be entrusted to Guangdong International Clinical Research Center of Chinese Medicine. We have added it to the revised manuscript.

11. TRIAL STATUS: Why only 53 patients (10% of target sample size) were recruited in two years? What's the recruiting plan for this trial in the coming years.
Answer: The study was started from November 2014. Meanwhile, a clinical study for the National Key Technology R&D Program for the 12th Five-year Plan of Ministry of Science and Technology (China, No. 2013BAI02B03) which we conducted was recruiting patients with psoriasis at the same time. That study focused on Chinese medicine combined with clcipotriol betamethasone and calcipotriol ointment for psoriasis. Most patients preferred to join the study for combined treatment. So, few patients were recruited in this double dummy trial. But now we can quicken the recruiting pace because the study for 12th Five-year Plan was drawing to an end.

Reviewer: 4
Reviewer Name: Mahmoud Rafieian-Kopaei
Institution and Country: Shahrekord University of Medical Sciences, Iran
Please state any competing interests: No Competing Interest to declare

Please leave your comments for the authors below

The manuscript is not sound enough and does not provide enough novelty to be published in BMJ Open.
Answer: Thank you for your comment. We will make determine efforts to improve this manuscript in order to provide enough novelty to be published.

Reviewer: 5
Reviewer Name: Raja Sivamani
Institution and Country: University of California, Davis, USA, California State University, Sacramento, USA
Please state any competing interests: Scientific Advisory Board for Dermveda, Inc

Please leave your comments for the authors below

The authors describes a clinical trial protocol that utilizes a double-dummy design to study the effects of PSORI-CM01 and Yinxieling on psoriasis. The PSORI-CM01 is a simplified version of Yinxieling and the authors would like to assess how it compares to Yinxieling. They plan to utilize reduction in PASI score at 12 weeks as their primary endpoint. This is a well-designed protocol and the authors should address the following points for further clarification:

1) Within Chinese medicine, there are several ways that imbalances can show up as Psoriasis. The authors need to be a better job of explaining why the Yinxieling was originally developed. What are the imbalances that develop in TCM that are being corrected by Yinxieling. Furthermore, what is the significance of removing the three herbs to make PSORI-CM01. The authors provide an explanation from a western pharmacological perspective but it is important that the TCM theory is not lost. Please provide a short paragraph explaining the TCM theory behind both Yinxieling and PSORI-CM01. This theory is particularly important because this study intends to compare PSORI-CM01 to Yinxieling and does not compare to a placebo. The weakness of this protocol is that we will not learn the absolute effectiveness of either treatment but will learn the relative effectiveness compared to each other.
Answer: In TCM theory, there are three syndromes of psoriasis: blood heat, blood stasis, and blood

dryness type. In the acute stage, the pathogenesis of psoriasis vulgaris is mostly blood heat obstructed on the surface of skin. In the chronic stage, the pathogenesis of psoriasis vulgaris is blood deficiency developed into dryness which cannot nourish skin, or blood stasis which obstruct blood flow running in skin collaterals. Therefore, activating blood circulation and removing blood stasis had given full play to the curing of psoriasis. Yinxieling tablet is playing the role of activating blood circulation and removing blood stasis in the treatment of psoriasis.
But considering too many blood-activiating and stasis-dissolving drugs would cause consumption of Qi, we removed angelica sinensis, radix rehmanniae recen, ligusticum wallichii from Yinxieling. The remain seven herbs turned to be PSORI-CM01.

2) The patients that are recruited need to be characterized from the TCM diagnostic point of view as well. Psoriasis is a western diagnosis (and I applaud the authors for using standard PASI based endpoints). However, the study also needs to include the TCM diagnostics for each recruited subject. Otherwise, we will lose the TCM theory and approach in the process that can be vital for subgroup analysis.
Answer: We will collect information about TCM syndromes before and after the treatment. The subgroup analysis will be performed based on the severity of disease and TCM syndromes.

3) Exclusion criteria #9 ((9) Patients need systemic treatment with western medicine) does not make sense. The inclusion criteria notes that subjects with a PASI between 3 to 30 are eligible. Those in the higher PASI scores would be eligible for systemic therapy and so exclusion #9 would contradict the inclusion criteria to include subjects up to a PASI for 30.
Answer: We agree the patients in severity psoriasis would be eligible for systemic therapy. So, exclusion #9 was deleted in the revised manuscript.

4) Those with psoriatic arthritis should be excluded as these subjects would require systemic treatment irrespective of PASI level.
Answer: We agree that psoriatic arthritis should be excluded in this study. We have added the words psoriatic arthritis in the exclusion criteria#2.

5) The primary outcome needs to be better detailed. The authors note that the primary outcome will be the reduction in the PASI score. This needs to be more specific since primary objectives are a singular timepoint. Perhaps, the authors meant to state that the primary outcome would be a reduction in the PASI score at 12 weeks.
Answer: We agree that the PASI reduction calculated at 12 weeks should be considered as the primary outcome. We are sorry we did not clarify it clearly before.

We have modified the description in Primary outcome section.

6) The sample size calculation portion is very poorly written and there are unfinished sentences along with poor English. The reasons for a one-sided two-sample t-test need to be better described. It seems that the intent of the study is to show that PSORI-CM01 is superior to Yinxieling at a significance of 0.025 alpha. If this is the case, the authors need to consider that it may be inferior to Yinxieling as well and should perform a two-sided two-sample t-test with an alpha of 0.05 so that they can capture both possibilities. Testing only one side appears biased and would prevent the authors from gathering otherwise valuable information.
Answer: It is really poorly written in sample size calculation section. We have rewritten this section in the revised manuscript.

7) The PASI score is a non-parametric score and he authors need to justify why they have chose the t-test which is reserved for parametric scores. The Wilcoxon signed-rank test would be more appropriate for comparing the PASI score unless the authors have otherwise compared the t-test and the Wilcoxon signed-rank. Nevertheless, the PASI is non-parametric and the authors need to account

for this in their primary outcome and their sample size calculations.
Answer: We tested whether the PASI score is a non-parametric score. The result showed that p value of normality test (KS test) was more than 0.1 (p=0.200). So, we considered that PASI score is a parametric score in statistical analysis.

8) The English has many grammatical errors that should be corrected. Answer: It is true that there are grammatical errors need to be corrected. We had sent the manuscript to AJE (American Journal Experts) for language service before submitting the revised version.

9) The authors should expand the discussion of their limitations. Limitations include:
a) There is no absolute placebo control, which means that they will not be able to assess absolute efficacy and only relative efficacy.
b) There is no stratification based on TCM diagnoses and the herbal formulations may be better suited for certain TCM imbalances than others within the psoriasis umbrella.
Answer: We would like to thank the reviewer once again for the suggestion on the limitations of this study. We have modified Limitations section in the revised manuscript with the reviewer's suggestion.

VERSION 2 – REVIEW

REVIEWER	Robert Gniadecki University of Alberta, Canada
REVIEW RETURNED	25-May-2017

GENERAL COMMENTS	No further comments

REVIEWER	Ying Zhang Beijing University of Chinese Medicine, China
REVIEW RETURNED	31-May-2017

GENERAL COMMENTS	Statistical method: "The various parameters observed will be compared using the chi-square test for non-continuous variables (i.e., the primary outcome and relapse rate), and t-tests and analyses of variance (ANOVAs) will be used for the continuous variables. " then how to deal with rank or skewed (not follow normality) data in these analyses?

REVIEWER	Raja Sivamani University of California, Davis California State University, Sacramento Scientific Advisory Board - Dermveda, Inc.
REVIEW RETURNED	09-Jun-2017

GENERAL COMMENTS	The authors have addressed all the concerns.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Robert Gniadecki
University of Alberta, Canada
Please state any competing interests or state ‘None declared’: None declared
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Please leave your comments for the authors below
No further comments

Response: We appreciate very much the remarks of the reviewers. The remarks will benefit the improvement of the paper and our future research.

Reviewer: 3
Ying Zhang
Beijing University of Chinese Medicine, China
Please state any competing interests or state ‘None declared’: None declared
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Please leave your comments for the authors below

Statistical method: "The various parameters observed will be compared using
the chi-square test for non-continuous variables (i.e., the primary outcome and relapse rate), and t-tests and analyses of variance (ANOVAs) will be used for the continuous variables. " then how to deal with rank or skewed (not follow normality) data in these analyses?

Response: Thank you for pointing this out. We have added the following explanations of the statistical method：Rank or skewed (not follow normality) data in these analyses will be examined using Wilcoxon signed-rank test.

Reviewer: 5
Raja Sivamani
University of California, Davis, California State University, Sacramento
Please state any competing interests or state ‘None declared’: Scientific Advisory Board - Dermveda, Inc.

Please leave your comments for the authors below
The authors have addressed all the concerns.

Response: We appreciate very much the remarks of the reviewers. The remarks will benefit the improvement of the paper and our future research.